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Health and Environmental Effects Profile for Acrylonitrile

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16. ABSTRACT

The Health and Environmental Effects Profile for acrylonitrile was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Acrylonitrile has been evaluated as a carcinogen. The human carcinogen potency factor (q_1*) for acrylonitrile is 5.4×10^{-1} $(mg/kg/day)^{-1}$ for oral exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for acrylonitrile is 100.

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR ACRYLONITRILE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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PREFACE

The health effects of acrylonitrile have been reviewed extensively in the Health Assessment Document for acrylonitrile (U.S. EPA, 1983a) and in another document prepared by the Syracuse Research Corporation (Neal and Tulles, 1983). Because the volume of literature available and the time constraints of this task, this HEEP has incorporated, with minor changes, verbatim portions of U.S. EPA (1983a) and Neal and Tullis (1983).

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LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
bw	Body weight
CAS	Chemical Abstract Service
CNS	Central nervous system
CS	Composite score
DNA	Deoxyribonucleic acid
EC_{50}	Median effective concentration
GSH	Reduced glutathione
GC/MS	Gas chromatography/mass spectrometry
HPLC	High performance liquid chromatography
i.p.	Intraperitoneal
i.v.	Intravenous
K_{oc}	Soil sorption coefficient standardized with respect to organic carbon
K_{ow}	Octanol/water partition coefficient
LC_{LO}	Lowest lethal concentration
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
MATC	Maximum acceptable toxicant concentration
MED	Minimum effective dose
NADPH	Nicotinamide adenine dinucleotide phosphate
ppb	Parts per billion
ppm	Parts per million
RNA	Ribonucleic acid
RQ	Reportable quantity
RV_d	Dose-rating value

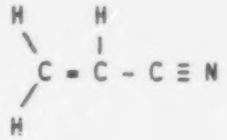
LIST OF ABBREVIATIONS (cont.)

RV_e	Effect-rating value
s.c.	Subcutaneous
TLV	Threshold limit value
TWA	Time-weighted average
UDP	Uridine diphosphate
v/v	Volume per volume

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Acrylonitrile is also known as AN, vinyl cyanide, 2-propenenitrile and cyanoethylene. The chemical structure and empirical formula are as follows:



Empirical formula: C_3H_3N

Molecular weight: 53.06

The CAS Registry number is 107-13-1.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Acrylonitrile is a clear, colorless liquid possessing a characteristic odor. It is soluble in water and miscible with organic solvents such as acetone, carbon tetrachloride, benzene, diethyl ether, petroleum ether and methyl alcohol (Groet and Badger, 1978). Selected physical properties are given in Table 1-1.

1.3. PRODUCTION DATA

Acrylonitrile is produced commercially by reacting vapor phase propylene, ammonia and air in the presence of a catalyst (Groet and Badger, 1978). The manufacturers of acrylonitrile are American Cyanamid in Arondale, LA, Dupont in Beaumont, TX, Monsanto Co. in Chocolate Bayou, TX, and Texas City, TX, and Sohio Chemical Co. in Greenlake, TX, and Lima, OH

TABLE 1-1

Selected Physical Properties of Acrylonitrile*

Property	Value
Boiling point at 1 atm:	77.3°C
Melting point:	-83.55°C
Density at 20°C:	0.806 g/cm^3
Vapor density (air = 1):	1.83
Vapor pressure at 23.6°C: at 45.5°C:	100 mm Hg 250 mm Hg
log K_{ow}:	-0.92
Water solubility at 25°C:	7.9×10^4 ppm
Henry's Law Constant at 25°C	8.8×10^{-5} atm-m^3/mole
Flash point, closed cup:	-4.4°C

*Sources: Groet and Badger, 1978; Miller and Villaume, 1978; Leo et al., 1971; Mabey et al., 1981

(Chemical Marketing Reporter, 1984). The market demand in 1983 for acrylonitrile was 2.146 billion pounds and the 1984 demand was predicted to be ~2.210 billion pounds (Chemical Marketing Reporter, 1984).

1.4. USE DATA

Acrylonitrile is used as a raw material in the manufacture of acrylic and modacrylic fibers, plastics, particularly acrylonitrile-butadiene-styrene (ABS) and styrene-acrylonitrile (SA) resins, nitrile rubbers and barrier resins, adiponitrile and acrylamide (Chemical Marketing Reporter, 1984). It has the following use pattern (Chemical Marketing Reporter, 1984):

exports	35%
acrylic and modacylic fibers	32%
ABS and SA resins	15%
adiponitrile	9%
acrylamide	4%
miscellaneous (including nitrile rubber and barrier resins)	5%

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

The fate of acrylonitrile depends upon its ability to undergo chemical, photochemical and biochemical degradation, volatilization and bioaccumulation. Acrylonitrile does not hydrolyze or dissociate appreciably in natural aquatic systems (Miller and Villaume, 1978; Mabey et al., 1981). Photochemical decomposition of isolated acrylonitrile in water may not be possible since the absorption maxima is ~250 nm (Grasselli and Ritchey, 1975); however, photolysis can occur in the presence of photosensitizers such as xanthene, triphenylene, benzophenone, acetophenone, fluorenone and dibromoanthracene (Basu et al., 1982).

Available data suggest that acrylonitrile is susceptible to biodegradation by microorganisms. Various studies indicate that aerobic bacteria, particularly acclimated microorganisms, are capable of degrading acrylonitrile (Cherry et al., 1956; Mills and Stack, 1955; Ludzack et al., 1958; Thom and Agg, 1975). Low concentrations of acrylonitrile can be decomposed anaerobically by microbial digestion (Ludzack et al., 1961; Lank and Wallace, 1970). Ludzack et al. (1958) studied the aerobic degradation of five 50 mg/ℓ samples of acrylonitrile in Ohio River water. After an initial acclimation period, rapid decomposition occurred. The acclimation time was affected by redosing, season and presence of activated sludge. Also, at low pH, microbe activity may be inhibited (Basu et al., 1982). Mills and Stack (1955) suggested that the biological oxidation of acrylonitrile proceeds by enzyme-catalyzed hydrolysis, producing ammonia and acrylic acid. In a study by Cherry et al. (1956), 10 ppm acrylonitrile decomposed completely in the Hackensack River water in 20 days; similar results were observed at concentrations of 25 and 50 ppm. In activated sludge, degradation was nearly complete after 20 days (NAS, 1975). Effective aerobic degradation in activated sludge has been studied at efficiencies of 90-97% (Ludzack et al., 1961), 100% (Tabak et al., 1981) and others (Slave et al., 1983; Stover and Kincannon, 1983; Ludzack et al., 1958; Institute of Microbiology, 1977). Kato and Yamamura (1976) reported that >90% of acrylonitrile was decomposed by Nocardia sp. Anaerobic decomposition in activated sludge may occur at low concentrations (Lank and Wallace, 1970), but at higher concentrations acrylonitrile has been determined to be inhibitory to some anaerobes (Miller and Villaume, 1978).

Barrows et al. (1980) experimentally measured a BCF of 48 in bluegill sunfish with a continual-flow apparatus. Estimation of BCF from water solubility (WS) and K_{ow} can be accomplished from the following equations: 1) log BCF = 2.791-0.564 log WS (in ppm) (Kenaga and Goring, 1980), and 2) log BCF = 0.76 log K_{ow} - 0.23 (Veith et al., 1980). The BCF values calculated from equations (1) and (2) are 1 (WS = 79000 ppm) and 0.3 (log K_{ow} = -0.92), respectively. The experimental BCF and the estimated BCFs indicate that bioaccumulation of acrylonitrile in aquatic organisms is not significant.

Data were not available regarding the transport of acrylonitrile from water, but its behavior can be predicted by correlating various physical properties. Mabey et al. (1981) calculated the Henry's Law constant for acrylonitrile, based on its vapor pressure and water solubility at 25°C, to be 8.8×10^{-5} atm-m^3/mole. This value of Henry's Law constant suggests that volatilization from environmental waters is likely to be significant, but probably not rapid (Lyman et al., 1982). The relatively high water solubility and low K_{ow} of acrylonitrile suggest that adsorption to particulate organic matter and sediment is not likely to be important.

2.2. AIR

Acrylonitrile may be removed from the atmosphere by reaction with atomic oxygen, hydroxyl radicals and ozone. The reaction half-life can be estimated using the following equation: $T_{1/2} = 0.6931/(K)(C)$, where K is the reaction rate constant and C is the radical concentration in the atmosphere (Lyman et al., 1982). Hydroxyl reaction half-life was calculated to be 2 days at 25°C using data from Harris et al. (1981) ($K = 4.04\times10^{-12}$ cm^3/molecule-sec) and an average atmospheric OH concentration of 10^6 molecules/cm^3. In a simulated smog chamber, the hydroxyl reaction half-life was determined to be 9 days (Suta, 1979).

Based on a reaction rate constant of 0.05×10^{-18} cm^3/molecule-sec (Cupitt, 1980), ozonolysis half-life was calculated to be 160 days. As a group, olefins react with atomic oxygen faster than any other class of compounds. Therefore, acrylonitrile, an olefin, may react with oxygen atoms in the atmosphere. Although no reference provided specific data for this reaction, the atomic oxygen-olefin reaction has a rate constant ~10 times greater than the hydroxyl-olefin rate constant (Basu et al., 1982). Acrylonitrile does not absorb light in the visible or near ultraviolet spectrum; therefore, direct photolysis of this compound does not occur (Callahan et al., 1979).

The half-lives of acrylonitrile in rainwater and adsorbed to aerosol particles have been predicted to be >0.8 years and 2.4x107 years, respectively (Cupitt, 1980). Based on this information, significant removal from the atmosphere by wet and dry deposition is not expected.

The time it takes a chemical to decompose to 1/c of its original quantity is called the atmospheric residence time. Cupitt (1980) projected an atmospheric residence time of 5.6 days for acrylonitrile. Joshi (1977), however, predicted a half-life of 9-10 hours. In as little as 9 hours extensive dispersion of acrylonitrile by aerial transport can occur. At an average wind speed of 4 m/sec, Suta (1979) estimated 86% survival of acrylonitrile 30 km downwind of a point source and 78% survival 50 km downwind.

2.3. SOIL

Few studies on the fate and transport of acrylonitrile in soil have been performed. Acrylonitrile can be decomposed by soil the fungi, Penicillum, Aspergillus and Cladosporium (Giacin 1973) and the microbe Nocardia rhodochrons LL100-21 (Digeronimo and Antoine, 1976). Kenaga (1980) predicted that acrylonitrile is mobile in soil, based on a water solubility of 75,000 ppm and a calculated K_{oc} of 9. Acrylonitrile may therefore partition into the water fraction of soil and leach into groundwater or be transported in water runoff. The high vapor pressure of acrylonitrile indicates that evaporation from dry soil surfaces may be expected to occur rapidly.

3. EXPOSURE

3.1. WATER

The U.S. EPA Storet data base reported monitoring data from 3760 sites. Acrylonitrile was detected in water samples collected upstream, downstream and at the discharge points of 11 industrial plants in concentrations ranging from $<1.0\times10^{-4}$ to 4.3 ppm (Going et al., 1979). Acrylonitrile was also detected in the effluent discharged from an acrylic fiber manufacturing plant at a concentration of 100 ppm and from chemical and latex manufacturing plants in Louisville, KY (IARC, 1979). Accidental spillage of acrylonitrile caused groundwater and stream contamination at two different locations (Miller and Villaume, 1978). Unquantified amounts of acrylonitrile have also been detected in drinking water (Basu et al., 1982) and drinking water supplies (Coleman et al., 1976).

3.2. FOOD

Potential sources of exposure to acrylonitrile are fish and shellfish, food containers and packaging materials, and foods fumigated with acrylonitrile-containing fumigants (Basu et al., 1982). Acrylonitrile was detected in shelled walnuts at levels of 0-8.5 mg/kg and in cereal at levels of 0.1 mg/ kg (IARC, 1979). A weighted average BCF of 30 has been calculated for all aquatic life consumed by Americans (U.S. EPA, 1980). Migration into beverages from containers composed of 3-5 ppm acrylonitrile monomer was measured at <0.005 mg/kg (Basu et al., 1982). Migration from vegetable oil and margarine containers could be as high as 37 ppb (Basu et al., 1982).

3.3. INHALATION

Potential sources of exposure to acrylonitrile in air are occupational environment, smoking, volatilization from clothing, furniture, etc., and manufacturing plant emissions (U.S. EPA, 1980). Poor ventilation caused concentrations of 3-20 mg/m³ in the air of an acrylic fiber plant (U.S. EPA, 1980) and >2 ppm in French factories involved in manufacturing and polymerization of acrylonitrile (Cicolella et al., 1981).

Measurement of ambient air near acrylonitrile user and producer plants revealed concentrations of <2.5-130 ppb (Howie and Koester, 1983). Emissions of acrylonitrile into the atmosphere in concentrations of 11.2-22.1 g/hour from acrylonitrile manufacturing plants have been reported (IARC, 1979). Atmospheric monitoring near 11 industrial plants revealed levels of acrylonitrile ranging from 0.1-325 μg/m³ (Going et al., 1979). In offgases from oil shale retort processing, acrylonitrile levels of 0.5-2 ppm and 54 ppm were measured (Sklarew and Hayes, 1984).

Otson et al. (1983) detected various levels of acrylonitrile ranging from 4.1-12.3 ppm in office air. Volatilization from commonly used products (glues, coloring pens, corrective fluid) was assumed to be the source of acrylonitrile. In cigarette smoke, acrylonitrile has been detected at levels of 1-2 mg/cigarette (IARC, 1979).

3.4. DERMAL

Absorption through skin is a possible route of exposure for workers involved in the manufacture and polymerization of acrylonitrile. Upon contact with the skin of the forearm, acrylonitrile is absorbed at a rate of 0.6 mg/cm²/hour (U.S. EPA, 1980). Other pertinent data regarding acrylonitrile monitoring for dermal exposure were not located in the available literature as cited in the Appendix.

4. PHARMACOKINETICS

4.1. ABSORPTION

Young et al. (1977) studied the pharmacokinetic and metabolic fate of acrylonitrile in male Sprague-Dawley rats by administering ^{14}C-acrylonitrile by different routes and dose levels. Acrylonitrile was absorbed extensively following oral administration to rats. After 72 hours, the percentage of recovered radioactivity accounted for 82±9.64% and 104±14.4% of the administered dose at 0.1 and 10 mg/kg, respectively (Table 4-1). The recovery of radioactivity in the urine was higher in animals administered the higher dose, while both doses resulted in a 5% recovery of radioactivity in the feces indicating that absorption was ~95%. When animals were exposed to acrylonitrile vapor in a "nose only" chamber at concentrations of 5 and 100 ppm (11 and 217 mg/m^3) for 6 hours, a significantly higher recovery was found in the urine at the higher dose, but a smaller percentage was recovered in the expired air as CO_2 and in the body (Table 4-2). For the inhalation study, the doses were estimated from the total recovered radioactivity to be 0.7 and 10.2 mg ^{14}C-acrylonitrile/kg, respectively.

The penetration rate of acrylonitrile vapor through the skin of rabbits was found to be 1% of that absorbed through the lungs (Rogaczewska, 1975).

4.2. DISTRIBUTION

Young et al. (1977) evaluated the plasma concentration of acryonitrile (μg Eq/mℓ plasma) as a function of time, route of administration (oral vs. i.v.) and dose level (0.1, 1 and 30 mg/kg). Following oral and intravenous administration of ^{14}C-acrylonitrile, typical plasma concentration vs. time curves were observed. The biphasic disappearance of radioactivity indicated a pharmacokinetic two-compartment open model for elimination. The half-life values of alpha and beta phases, calculated by linear regression analysis, ranged from 3.5-5.8 hours and 50-77 hours, respectively.

TABLE 4-1

Recovery of Radioactivity from Rats Given Single Oral Doses of 0.1 or 10 mg/kg ^{14}C-Acrylonitrile[a,b]

	Percentage of Dose, Mean ± S.D.	
Recovery Sites	(0.1 mg/kg)	(10 mg/kg)
Radioactivity in Urine	34.22±6.26[c]	66.68±10.60[c]
Radioactivity in Feces	5.36±1.43	5.22±1.17
Expired Air		
Organics in carbon[d]	0.09±0.09	0.11±0.06
Organics in solvent[e]	0.19±0.19	0.20±0.16
$H^{14}CN$[f]	0.07±0.05	0.08±0.03
$^{14}CO_2$[g]	4.56±1.82	3.93±1.79
Body	37.02±6.09[c]	26.61±5.91[c]
Carcass	24.24±5.02[c]	16.04±1.87[c]
Skin	12.78±1.17	10.57±4.55
Cage Wash[h]	0.86±0.37	1.22±0.41
Total Recovery[i]	82.37±9.64[c]	104.04±14.40[c]

[a] Source: Young et al., 1977

[b] Two groups of rats housed individually in glass metabolism cages were given 0.1 mg/kg (4 rats) or 10 mg/kg (5 rats); excreta were collected at 8 hour intervals for 72 hours.

[c] The mean values for the two dose levels are different at the $p=0.05$ level of significance.

[d] Pittsburg activated coconut charcoal, 12x30 mesh.

[e] Trap = 2-methoxyethanol

[f] Trap = 0.02 M Ag_2SO_4 in 0.1 N H_2SO_4

[g] Trap = 5 M ethanolamine in 2-methoxyethanol

[h] Water-acetone

[i] The mean and S.D. of the recovery were calculated from the total recovery of the dose in individual rats.

S.D. = Standard deviation

TABLE 4-2

Recovery of Radioactivity from Rats Exposed by Inhalation to 5 or 100 ppm ^{14}C-Acrylonitrile for 6 hours[a,b]

Recovery Sites	Percentage of Recovered Dose[c]	
	(5 ppm)	(100 ppm)
Urine	68.50±9.38[d]	82.17±4.21[d]
Feces	3.94±0.97	3.15±0.82
$^{14}CO_2$	6.07±1.58[d]	2.60±0.83[d]
Body	18.53±4.68[d]	11.24±2.85[d]
Cage Wash	2.95±3.95	0.85±0.58

[a] Source: Young et al., 1977

[b] Rats were exposed in a "nose only" chamber under dynamic air flow conditions for 6 hours. After exposure, rats were housed in glass metabolism cages and excreta were collected for 220 hours.

[c] Values are the mean ± S.D. for 4 rats per exposure level.

[d] The mean values for the two exposure levels are different at the p=0.05 level of significance.

S.D. = Standard diviation

Freshour et al. (1980) investigated the pharmacokinetic profile of acrylonitrile after its i.v. or oral administration to male F344 rats. The plasma concentration of acrylonitrile vs. time curve obtained after i.v. administration was characteristic of a one-compartment model with first-order elimination, but biphasic elimination was observed following a 30 mg/kg oral dose. The half-life of first-order elimination ranged from 7.8-13.9 minutes after 30 mg/kg i.v. and oral doses, and the half-life for the terminal phase after 30 mg/kg oral administration was 85-120 minutes.

Hashimoto and Kanai (1965) evaluated the blood concentrations of acrylonitrile and cyanide as a function of time in relation to toxicity. Acrylonitrile was eliminated biphasically with 1 μg/mℓ remaining after 4 hours, when administered intravenously to rabbits at a sublethal dose of 30 mg/kg (LD_{50}=50 mg/kg). Ahmed and Patel (1981) observed maximum blood cyanide concentrations 1 hour after dosing in mice but at 3 hours in rats, indicating a species difference in metabolism.

Following a single oral or intravenous dose to rats at 0.1 and 10 mg/kg, acrylonitrile and its metabolites were distributed to all tissues examined (Young et al., 1977). Regardless of the route of exposure or dose level, high levels of radioactivity were observed in the stomach, skin and red blood cells (Table 4-3). The accumulation of radioactivity in the stomach wall was high after both intravenous and oral administration, indicating that the accumulation was not due to poor absorption. Following an intravenous dose, the radioactivity increased from 30.33 μg Eq at 5 minutes to 68.64 μg Eq at 24 hours. Young et al. (1977) concluded that the retention of acrylonitrile and its metabolites in the stomach was due in part to enterogastric circulation. Others concluded that the accumulation of radioactivity in the blood was due primarily to covalent binding of acrylonitrile

TABLE 4-3

Distribution of Radioactivity in Selected Tissues of Rats Given ^{14}C-Acrylonitrile[a]

Tissue	Tissue to Plasma Ratios of ^{14}C-Activity			
	i.v.[b]		per os[c]	
	2 hours (1 mg/kg)	24 hours (1 mg/kg)	72 hours (0.1 mg/kg)	(10 mg/kg)
Lungs	0.96	1.07	0.87	0.96
Liver	0.68	1.20	0.57	0.84
Kidneys	1.33	3.15	0.83	1.08
Stomach Wall and Contents	8.11	7.36	14.28	11.26
Intestines	0.72	0.31	1.06	0.99
Duodenum	0.85	0.68	NA	NA
Jejunum	0.92	0.57	NA	NA
Ileum	1.01	0.44	NA	NA
Cecum	0.37	0.07	NA	NA
Colon	0.51	0.07	NA	NA
Skeletal Muscle	NA	0.50	0.35	0.41
Heart	0.64	0.78	NA	NA
Spleen	0.98	NA	NA	NA
Brain	0.65	0.76	NA	NA
Thymus	0.74	NA	NA	NA
Testes	0.67	NA	NA	NA
Skin	1.91	2.85	2.10	2.70

TABLE 4-3 (cont.)

Tissue	Tissue to Plasma Ratios of ^{14}C-Activity			
	i.v.[b]		per os[c]	
	2 hours (1 mg/kg)	24 hours (1 mg/kg)	72 hours (0.1 mg/kg)	(10 mg/kg)
Carcass	0.54	0.73	0.71	0.55
Packed Blood Cells	3.33	7.16	2.26[d]	5.73[e]
Plasma Concentration (μg Eq/mℓ)	0.727	0.220	0.022	1.437

[a] Source: Young et al., 1977

[b] One rat per time.

[c] Average of 2 rats per dose.

[d] For all 4 rats in this group, the ratio was 2.18±0.20 (Mean ± SD)

[e] For all 5 rats in this group, the ratio was 5.16±1.19 (Mean ± SD)

NA = Not analyzed; S.D. = Standard deviation to macromolecules and lipids in the red blood cells (Ahmed and Patel, 1979; Ahmed et al., 1982). In other tissues, the amount of radioactivity declined rapidly with time because of excretion (Young et al., 1977; Ahmed and Patel, 1979; Ahmed et al., 1982).

Using the technique of whole-body autoradiography after ^{14}C-acrylonitrile administration to rats and monkeys, similar distribution patterns were obtained (Sandberg and Slanina, 1980). Male and female rats were sacrificed 1 minute, 20 minutes, 1 hour, 4 hours, and 7 days after i.v. treatment of 13 mg/kg acrylonitrile. Two monkeys were sacrificed 1 and 6 hours, after oral doses of 4 or 6 mg/kg, respectively. There was no difference in the distribution pattern of acrylonitrile between the two routes of adminis- tration, except for a slower absorption time following oral dosing. The labeling pattern was similar in rats and monkeys, except for more activity in the liver. High levels of activity were present in the blood and excre- tory pathways (bile, intestinal contents and urine) with the liver, kidney, lung and adrenal cortex also accumulating appreciable amounts of label. The stomach and hair follicles showed constant uptake of label throughout the study. Radioactivity was present in animals killed 7 days after administration of acrylonitrile. In fetuses exposed in utero, only the eye lens accumulated a higher concentration of label than that observed in maternal blood.

Sapota (1982) compared the disposition of [1,2-^{14}C] acrylonitrile or acrylo[^{14}C]nitrile administered intraperitoneally or orally to Wistar rats. Most of the label was associated with erythrocytes, liver and kidneys, with loss of ^{14}C from the erythrocytes occurring more slowly than from the liver or kidney. One hour after dosing, lower levels of ^{14}C from acrylo[^{14}C]nitrile were found in the plasma and higher levels in the spleen and brain than label from [1,2-^{14}C] acrylonitrile. No other differences were observed in distribution of the label.

Jaeger et al. (1984) determined the tissue distribution of ^{14}C-acrylonitrile in rats given a standard diet, a casein-based diet and 2 diets high in saturated fat content that were lipotrope-deficient or lipotrope-supplemented. Diet had no effect on the distribution of radioactivity in the tissue. The sequence of tissue activity (nCi^{14}C/g or mℓ) was as follows: blood>stomach>liver,duodenum,lung,kidney>brain>adrenal.

The highest levels of radioactivity were detected in the blood, lung, liver and kidney of male Sprague-Dawley rats given a single i.p. injection of 10 mg/kg [2,3-^{14}C] acrylonitrile (Sato et al., 1982). Radioactivity was detected in all subcellular fractions, with the highest levels occurring in the cytosol and mitochondrial fractions (Table 4-4).

Ahmed et al. (1982, 1983) studied the distribution of [1-^{14}C] acrylonitrile and [2,3-^{14}C] acrylonitrile following a single oral dose of 46.5 mg/kg to male Sprague-Dawley rats. The red blood cells retained significant amounts of radioactivity from both compounds for >10 days, whereas the ^{14}C activity in plasma declined sharply. The highest level of radioactivity from both compounds was recovered in the gastrointestinal tract. Radioactivity in the acid soluble fractions in the liver, kidney, brain, spleen, adrenal, lung and heart declined sharply, while radioactivity associated with macromolecules remained unchanged. Of the total radioactivity, 24% was bound to nuclear, mitochondrial and microsomal fractions, while only 6-14% was bound in the cytosol. The percentage of covalent binding of [2,3-^{14}C] acrylonitrile was significantly higher than [1-^{14}C] acrylonitrile, even 72 hours after dosing.

TABLE 4-4

Distribution of ^{14}C Radioactivity in Subcellular Fractions of Selected Tissues of Rats After a Single i.p. Injection of 10 mg Acrylonitrile/kg Body Weight[a]

Fraction	Specific radioactivity (dpm/mg protein)[b]					
	1 day after an injection			3 days after an injection		
	Brain	Liver	Kidney	Brain	Liver	Kidney
Total homogenate	190	242	219	132	95.0	137
Heavy mitochondria	202	252	171	199	99.5	96.4
Light mitochondria	140	263	647	245	109	91.5
Microsome	151	136	292	99.4	62.9	68.9
Cytosol	251	96.5	465	151	176	176

[a] Source: Sato et al., 1982

[b] Each value indicates the mean from three rats.

The binding of [3-^{14}C] acrylonitrile to cellular portions can result from direct alkylation by acrylonitrile; however, the extent of binding can be increased by microsomal activation, (Duverger-Van Bogaert et al., 1981). Peter et al. (1983) also found that binding of [2,3-^{14}C] acrylonitrile to DNA, RNA or bovine serum albumin was lowered when incubations were performed without microsomes. The authors concluded that acrylonitrile can alkylate nucleic acids, but the extent of irreversible binding was quantitatively less than that observed with vinyl halides. Solomon et al. (1984) also demonstrated that acrylonitrile can directly alkylate DNA in vitro at a physiological pH and temperature.

The irreversible binding of [2,3-^{14}C] acrylonitrile in vivo to nucleic acids and proteins from tissues of male Sprague-Dawley rats was studied after a single oral dose of 46.5 mg/kg (Farooqui and Ahmed, 1983). Binding of acrylonitrile to proteins was extensive and time-dependent. Radioactivity in nucleic acids was found primarily in the liver, stomach and brain. DNA alkylation was significantly higher in the brain and stomach (119 and 81 pmol/mg, respectively, at 24 hours) than in the liver (20 pmol/mg). The covalent binding indices for the liver, stomach and brain at 24 hours after dosing were 5.9, 51.9 and 65.3, respectively.

4.3. METABOLISM

Brieger et al. (1952) suggested that acrylonitrile is metabolized to cyanide, which is then transformed to thiocyanate and eliminated in the urine. Gut et al. (1975) and Hashimoto and Kanai (1965) demonstrated that <1/3 of an administered dose can be accounted for by this metabolic route. Acrylonitrile reacts with sulfhydryl groups through cyanoethylation, which prevents further metabolism to cyanide and thiocyanate (Hashimoto and Kanai, 1965). Other metabolic pathways have been suggested including formation of mercapturic acid (U.S. EPA, 1980), oxidation to CO_2 with cyanate ion (Boxer and Richards, 1952) and conjugation with D-glucuronic acid (Hoffman et al., 1976). Evidence from Gut et al. (1975), Wright (1977), Young et al. (1977), Ahmed and Patel (1981) and Geiger et al. (1983) suggested that the metabolism of acrylonitrile in mammals was related to dose level, route of administration and species.

4.3.1. Metabolism to Cyanide and Thiocyanate. Ahmed and Abreu (1982) demonstrated that acrylonitrile is converted to cyanide in the brain and liver of rats by enzymes associated with the microsomal fraction.

Nerudova et al. (1978) and Silver et al. (1982a) evaluated the effect of the route of administration on the biotransformation of acrylonitrile. Nerudova et al. (1979) found that 25, 2-5 and 1% of the dose was excreted in the urine as thiocyanate following oral, i.p. or i.v. administration, respectively. Pretreatment with antibiotics did not affect the extent of excretion following oral administration. Silver et al. (1982a) concluded that the length of the carbon chain, presence of substituents at the α-carbon, position of double bonds and route of administration were all important factors influencing the release of cyanide from nitriles.

Gut et al. (1975) studied the conversion of acrylonitrile to thiocyanate in three species (female Wistar rats, albino mice and Chinese hamsters). In rats, the thiocyanate excretion was higher after oral dosing (14.6-33.1%) than after i.p. (2.2-5.7%), s.c. (4.6%) or i.v. (1.2%) injection. Thiocyanate excretion showed a lag period of 4 hours after oral dosing. Similar results were also obtained for mice. More thiocyanate was excreted after oral dosing (35%) than after i.p. (8-10%) and i.v. (11%) injection. Excretion patterns for hamsters were also similar to rats and mice. In mice and hamsters, no lag period occurred after oral dosing of acrylonitrile. Gut et al. (1975) suggested that body size may be related to the occurrence of the lag period.

Gut et al. (1975) found that pretreatment of rats with phenobarbital, SKF525-A, cysteine or dimercaprol did not effect the excretion of thiocyanate after acrylonitrile dosing. Simultaneous i.p. administration of thiosulfate and acrylonitrile to rats and mice increased thiocyanate elimination 2-fold in rats and 3-fold in mice, but no effect of thiosulfate was observed after oral administration. The authors suggested that the lack of effect of microsomal enzyme induction or inhibition on acrylonitrile thiocyanate balance indicated that the route-dependent difference in thiocyanate elimination is caused by factors affecting the tissue distribution of acrylonitrile.

4.3.2. Reaction with Sulfhydryl Groups. In laboratory animals, acrylonitrile reacts with sulfhydryl compounds through cyanoethylation (Hashimoto and Kanai, 1965; Gut et al., 1975); the reaction products are not metabolized further and are excreted unchanged (Gut et al., 1975). Rapid decreases (within 4 hours) in the levels of glutathione in the liver and brain of hamsters have been observed following i.p. injection of acrylonitrile (Zitting et al., 1981). Hashimoto and Kanai (1965) showed that acrylonitrile rapidly forms stable conjugates _in vitro_ with materials that have active hydrogen atoms such as L-cysteine and L-glutathione. The formation of cysteine conjugates _in vivo_ was also demonstrated and the chemical structures of the metabolites were identified as S-(2-cyanoethyl) cysteine and N-acethyl-S-(2-cyanoethyl) cysteine (cyanoethylated mercapturic acid) (Gut et al., 1975).

Boyland and Chasseaud (1967) suggested that acrylonitrile reacts _in vitro_ with GSH by GSH transferase, but the conjugation was determined indirectly by measuring the disappearance of GSH substrates. U.S. EPA (1980) confirmed the presence of cyanoethylated mercapturic acid in rat urine. A proposed scheme for the various metabolic pathways of acrylonitrile biotransformation is presented in Figure 4-1.

Langvardt et al. (1980) detected seven urinary metabolites of acrylonitrile by HPLC in rats following oral administration of 30 mg/kg acrylonitrile . Of the seven metabolites, three major metabolites (metabolites 1, 6 and 7) were further identified by retention times and fragmentation patterns on GC-MS. Metabolite 1 was identified as thiocyanate, metabolite 7 as N-acetyl-S-(2-cyanoethyl) cystein, and metabolite 6 was identified tentatively as N-acety-3-carboxy-5-cyanotetrahydro-1,4-2H-thiazine. By analogy to known metabolic pathways for other halogenated vinyl compounds, Langvardt et al. (1980) proposed a possible metabolic pathway for acrylonitrile which proceeds through the formation of an epoxide intermediate (Figure 4-2).

Abreu and Ahmed (1980) demonstrated *in vitro* that rat liver microsomes plus NADPH were capable of forming cyanide from acrylonitrile. The production of cyanide increased when rat microsomal fractions induced with phenobarbital or Aroclor 1254 were used, while addition of SKF525-A to the reaction mixture inhibited the formation of cyanide. The results were consistent with a metabolic pathway proceeding through the formation of an epoxide intermediate.

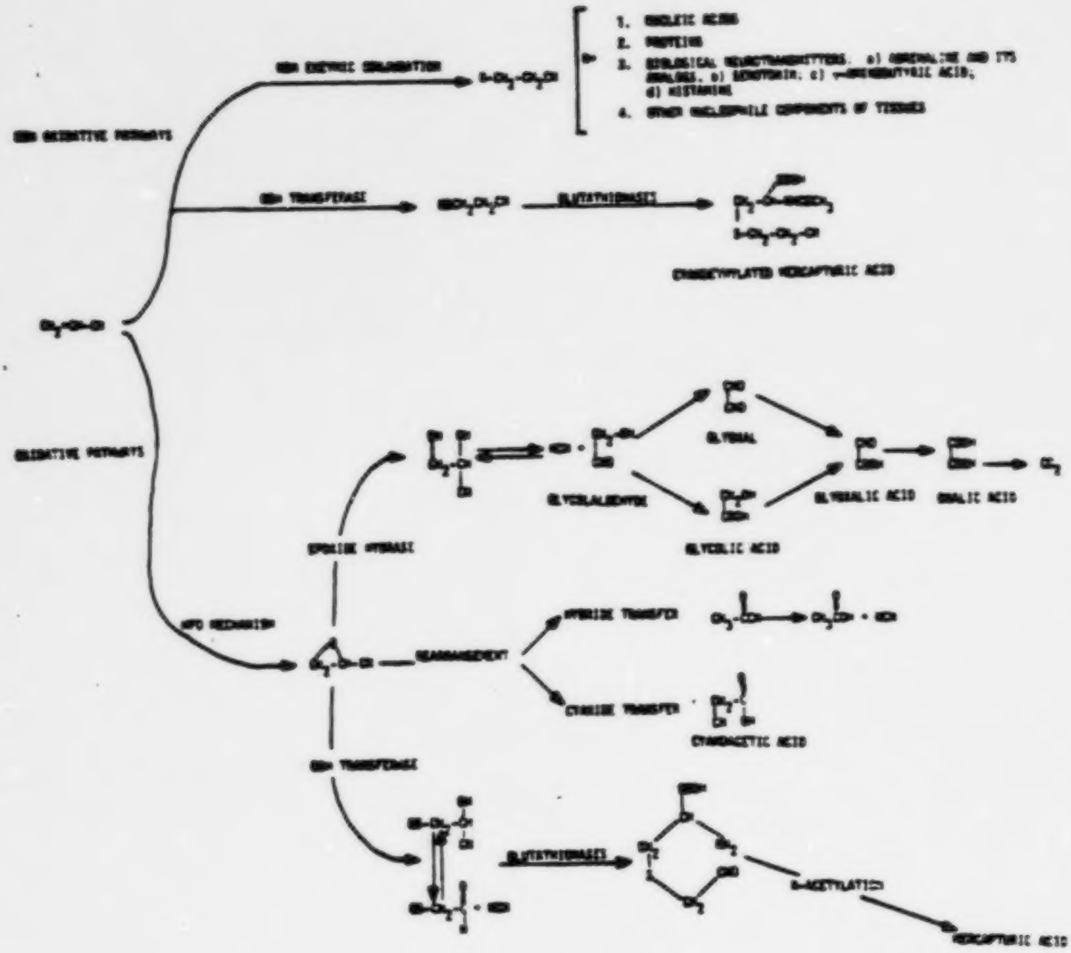
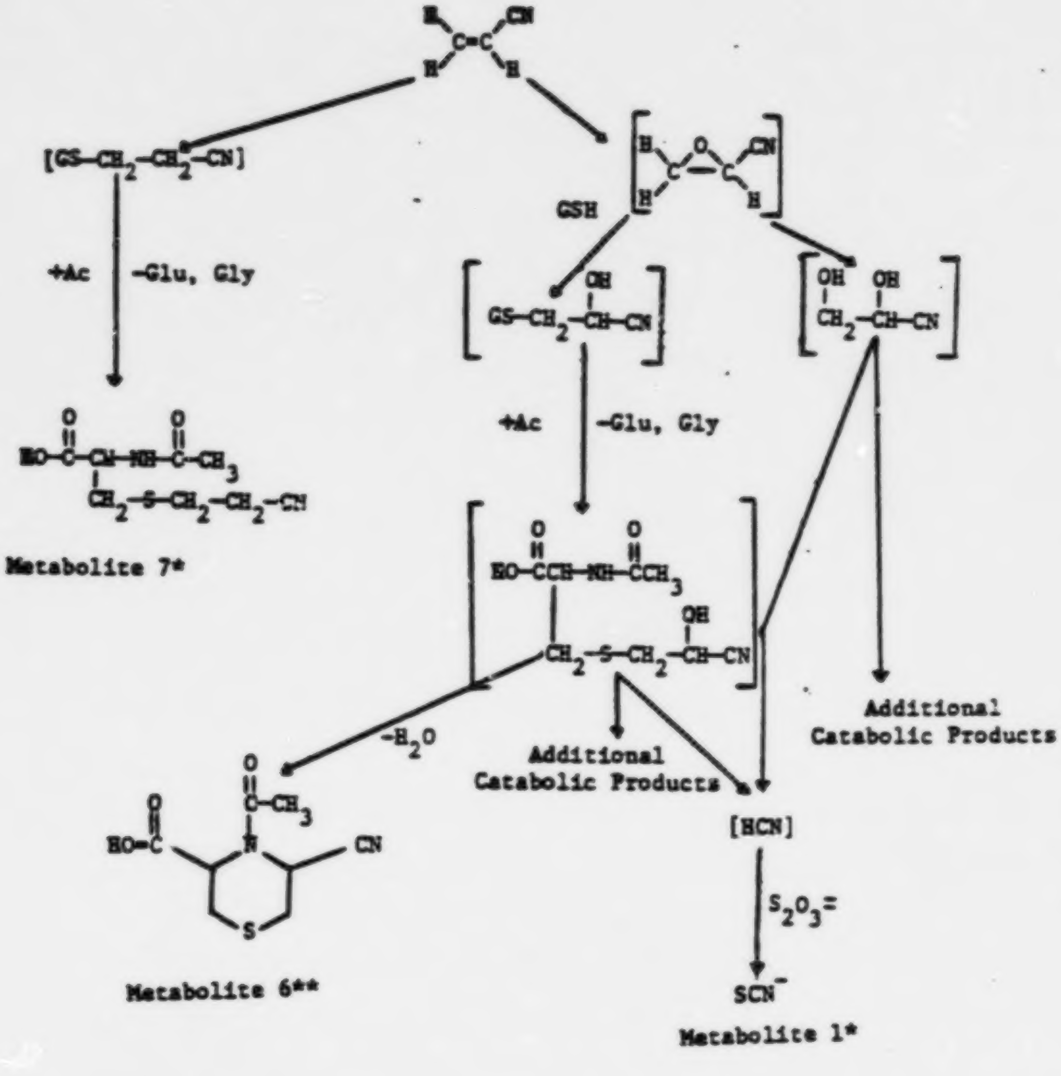


FIGURE 4-1

Proposed Pathways for Acrylonitrile Biotransformation

(U.S. EPA, 1980)


[GS–CH$_2$–CH$_2$–CN]
GSH
+Ac
–Glu, Gly
+Ac
–Glu, Gly
Metabolite 7*
–H$_2$O
Additional Catabolic Products
Additional Catabolic Products
[HCN]
S$_2$O$_3$=
SCN$^-$
Metabolite 6**
Metabolite 1*

*Confirmed Assignment
**Tentative Assignment
[ ]Hypothetical Assignment

FIGURE 4-2

Proposed Scheme for Metabolism of Acrylonitrile by the Rat

(Langvardt et al., 1980)

In a similar study, Guengerich et al. (1981) incubated rat liver microsomes with [1-^{14}C] or [2,3-^{14}C] acrylonitrile and isolated labeled compounds that cochromatographed on HPLC with 2-cyanoethylene oxide. The formation of the epoxide was enhanced by the inhibition of epoxide hydrolase. The addition of epoxide hydrolase to a solution of 0.5 mM 2-cyanoethylene oxide resulted in the destruction of the epoxide at a rate of 1.7 mmol/minute and the formation of HCN. Both acrylonitrile and 2-cyanoethylene oxide when mixed with GSH reacted nonenzymatically, and HCN was released in the reaction with the epoxide. The epoxide reacted less rapidly than did acrylonitrile in the system; however, when a cytosol preparation from rat liver was used, the rate of GSH conjugate formation was 309 and 31 mmol/mg/minute, respectively, for 2-cyanoethylene oxide and acrylonitrile. Cytosol preparations from the rat brain and human liver had no detectable GSH activity toward acrylonitrile, but did exhibit some activity toward 2-cyanoethylene oxide, although the activity was diminished by more than one order of magnitude when compared with that in the rat liver cytosolic preparation. A metabolite with a mass spectrum similar to one identified by Langvardt et al. (1980) was obtained by the nonenzymatic reaction of 2-cyanoethylene oxide with N-acetylcysteine. The metabolite was identified as 4-acetyl-3-carboxy-5-cyanotetrahydro-1,4-2H-thiazide. The Guengerich et al. (1981) study supports the metabolic pathway in which acrylonitrile is metabolized by microsomal enzymes to HCN through an epoxide intermediate. The study by Langvardt et al. (1980) also demonstrated that 2-cyanoethylene oxide binds nonenzymatically to both protein and DNA and that acrylonitrile did not, indicating that the 2-cyanoethylene oxide may be an important metabolite in the toxicity of acrylonitrile. Guengerich et al. (1981) found no conclusive evidence of metabolically mediated binding of acrylonitrile to protein and DNA in human systems.

4.3.3. Minor Metabolites. In addition to the cyanide and thiocyanate formed by acrylonitrile metabolism, acrylonitrile-glucuronide was formed and excreted in rat urine. Hoffman et al. (1976) suggested that acrylonitrile is initially hydrolyzed, and then undergoes a condensation reaction with UDP- glucuronic acid. Young et al. (1977) identified CO_2 as a metabolite of acrylonitrile and demonstrated that CO_2 accounted for 5-6% of an adminis- tered dose of acrylonitrile. Boxer and Richards (1952) demonstrated that the cyanide and thiocyanate carbon are oxidized directly to CO_2. Hashimoto and Kanai (1965) and Hoffman et al. (1976) estimated that ≈15% of an administered dose of acrylonitrile is eliminated unchanged in the urine and expired air.

4.3.4. Route and Dose Dependence of Acrylonitrile Metabolism. The metabolic fate of acrylonitrile and its dependence on dose level and route of administration have been studied by several researchers (Gut et al., 1975; Wright, 1977; Young et al., 1977). In rats, Wright (1977) observed that a lower dose (0.1 mg/kg) of acrylonitrile resulted in a greater portion of the dose being metabolized to cysteine conjugates (90%); however, a higher dose (30 mg/kg) resulted in a greater portion of the dose being excreted as thiocyanate and an unidentified metabolite "C." No differences were observed in the proportion of metabolities excreted in the urine by rhesus monkeys following administration of 0.1 and 30 mg/kg of acrylonitrile. Young et al. (1977) quantitatively isolated three metabolites (A, C and E) and CO_2 in male Sprague-Dawley rates given doses of acrylonitrile by several routes. Chemical structures of the metabolites were not identified. As noted in Table 4-5, the proportion of the metabolites in various rat fluids was route- and dose-dependent. The 0-72 hour urine sample showed the highest amount of metabolite C (73%) after an oral dose of

TABLE 4-5

Metabolites of ^{14}C-Acrylonitrile Separated from Various Fluids of Rats by HPLC[a]

Sample	Percentage of Total ^{14}C[b]		
	A	C	E
Urine, 0-72 hours			
0.1 mg/kg, per os	12	73	15
10.0 mg/kg, per os	61	8	32
5 ppm	9	30	61
100 ppm	32	33	35
Bile[c], 1 hour	2	91	1
In vitro[d]	17	78	1
Stomach[c,e], 24 hours	4	3	93
Red blood cells[c,e], 24 hours	7	10	83
Plasma[c], 24 hours	28	28	42

[a] Source: Young et al., 1977

[b] Metabolites A, C and E were the major metabolites separated by HPLC. Values are expressed as percentages of the total radioactivity in each sample applied to the column. The total percentages of A, C and E are <100% when minor metabolites B and D are present.

[c] A dose of 1 mg ^{14}C-acrylonitrile/kg was given intravenously.

[d] Metabolites extracted from reaction mixtures with ethanol. The source of enzyme was rat liver 9000 x g supernatant fluid.

[e] Ethanol extracts of stomach or red blood cells. About 80% of the radioactivity was extracted.

0.1 mg/kg, but the maximum amount of metabolite A (61%) was observed after an oral dose of 10 mg/kg. When rats were exposed to acrylonitrile vapor at a concentration of 5 ppm (11 mg/m³) for 6 hours, 61% of metabolite E was excreted in the urine, while a concentration of 100 ppm (217 mg/m³) resulted in equal proportions of the three metabolites. The predominant metabolite excreted in bile after a 1 mg/kg intravenous dose was metabolite C (91%). Metabolite E accounted for 93, 83 and 42% of the total radioactivity for the stomach, red blood cells and plasma, respectively.

4.4. EXCRETION

Ahmed et al. (1982) reported that rats administered an oral dose of 46.5 mg [1-^{14}C] acrylonitrile/kg excreted 40% of the administered radioactivity in the urine, 2% in the feces, 9% in expired air as $^{14}CO_2$, 0.5% as $H^{14}CN$ and 4.8% as unchanged acrylonitrile within 24 hours. Bile flow increased 3-fold after administration of acrylonitrile. In bile duct cannulated rats, 27% of the administered ^{14}C was recovered in the bile, indicating that enterohepatic recirculation occurs extensively.

Ghanayen and Ahmed (1982) studied the biliary excretion of [1-^{14}C] acrylonitrile. Bile-duct cannulated Sprague-Dawley rats excreted 27% of an oral dose of 46.5 mg/kg acrylonitrile in the bile within 6 hours. Phenobarbital pretreatment produced no change in biliary excretion; however, diethyl maleate pretreatment significantly decreased the portion of the dose excreted in the bile (6%) indicating the importance of GSH in acrylonitrile biotransformation. Two major biliary metabolites of acrylonitrile were found to be glutathione conjugates.

Gut et al. (1981) found that the elimination of thiocyanate was affected by the route of administration, but the elimination of the sum of the radioactive metabolites was not. The elimination of thiocyanate was higher after oral dosing (23% of the dose) than after i.p. (4%), s.c. (4.6%) or i.v. (1.2%) administration. Excretion of thiocyanate peaked between 8 and 14 hours after oral or i.p. administration, whereas the elimination of the sum of radioactive metabolites was highest in the first 4 hours after acrylonitrile administration. Regardless of the route of administration, <1% of the dose was recovered in the feces.

5. EFFECTS

5.1. CARCINOGENICITY

In a study conducted by Dow Chemical Company, Quast et al. (1980a) exposed Sprague-Dawley rats (48 rats/sex/treatment group and 80 rats/sex in the control group) to drinking water containing 35, 85 and 210 ppm acrylonitrile. After the first 21 days, the concentrations of acrylonitrile were changed to 35, 100 and 300 ppm. The calculated amount of acrylonitrile ingested was 3.42, 8.53 and 21.18 mg/kg/day for male rats and 4.36, 10.76 and 24.97 mg/kg/day for female rats. After 9 months of treatment, the rats at the two highest dose levels had rough hair coats and an unthrifty appearance. Treatment-related early mortality occurred in female rats at all exposure levels and in male rats at the highest exposure levels (Table 5-1). The differences in male and female mortality may be partially related to the larger doses of acrylonitrile ingested by female rats. The incidences of tumors in Sprague-Dawley rats are presented in Table 5-2.

Bio/dynamics Inc. (1980a,b,c) performed three studies with acrylonitrile for Monsanto Company. In the first study, Spartan rats (100 males and 100 females per group) were exposed to drinking water containing 1 and 100 ppm acrylonitrile. The daily intakes of acrylonitrile at the 1 ppm level were 0.093 and 0.146 mg/kg/day for males and females, respectively, and at the 100 ppm level were 7.98 and 10.69 mg/kg/ day, for males and females, respectively. The study was terminated after 19 months for females and 22 months for males. In the second study, Fischer 344 rats (100 animals of each sex per group, except controls which consisted of 200 animals of each sex) were exposed to 1, 3, 10, 30 and 100 ppm of acrylonitrile in the drinking water (Bio/dynamics Inc., 1980b). The average amount of acrylonitrile ingested for male rats was 0.08, 0.25, 0.84, 2.49 and 8.37 mg/kg/day,

TABLE 5-1

Cumulative Mortality of Male and Female Rats Maintained for 2 Years on Drinking Water Containing Acrylonitrile[a]

Days on Test	Percent Dead							
	Control		35 ppm		100 ppm		300 ppm	
	Male	Female	Male	Female	Male	Female	Male	Female
0-30	0	0	0	0	0	0	0	0
31-60	0	0	0	0	0	0	0	0
61-90	0	0	0	0	0	0	0	0
91-120	0	0	0	0	2.1	0	0	0
121-150	0	0	0	0	2.1	0	0	2.1
151-180	1.3	0	0	0	2.1	0	0	2.1
181-210	1.3	1.3	2.1	0	2.1	2.1	0	2.1
211-240	1.3	1.3	2.1	0	2.1	2.1	0	2.1
241-270	2.5	1.3	2.1	0	2.1	4.2	4.2	6.3
271-300	3.8	1.3	2.1	0	2.1	6.3	4.2	8.3
301-330	7.5	1.3	4.3	2.1	2.1	6.3	4.2	18.8[b]
331-360	8.8	1.3	4.3	2.1	2.1	6.3	8.3	29.2[b]
361-390	8.8	1.3	6.4	6.3	2.1	10.4[b]	14.6	33.3[b]
391-420	10.0	3.8	10.6	6.3	4.2	12.5	16.7	41.7[b]
421-450	13.8	3.8	14.9	10.4	10.4	12.5	22.9	50.0[b]
451-480	18.8	7.5	17.0	14.6	14.6	22.9[b]	31.3	64.6[b]
481-510	26.3	11.3	27.7	20.8	22.9	27.1[b]	45.8[b]	72.9[b]
511-540	26.3	13.8	29.8	25.0	33.3	35.4[b]	60.4[b]	77.1[b]
541-570	41.3	22.5	42.6	41.7[b]	37.5	56.3[b]	66.7[b]	87.5[b]
571-600	50.0	27.5	48.9	50.0[b]	47.9	70.8[b]	70.8[b]	93.8[b]
601-630	60.0	42.5	57.4	56.3	54.2	79.2[b]	77.1[b]	95.8[b]
631-660	67.5	46.3	70.2	68.8[b]	68.8	87.5[b]	83.3[b]	95.8[b]
661-690	83.8	56.3	83.0	79.2[b]	72.9	91.7[b]	100.0[b]	100.0[b]
691-720	87.5	67.5	87.2	87.5[b]	83.3	95.8[b]	100.0[b]	100.0[b]
721-745	91.3	75.0	89.4	91.7[b]	89.6	97.9[b]	100.0[b]	100.0[b]
Total Number of rats	80	80	47	48	48	48	48	48

[a] Source: Quast et al., 1980a

[b] Significantly different from controls by Fisher's Exact Probability Test, $p<0.05$.

TABLE 5-2

Tumor Incidence in Sprague-Dawley Rats Treated Orally with Acrylonitrile[a]

Sex	Dose or Exposure (mg/kg/day[b])	Duration of Treatment (months)	Purity of Compound[c]	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)[d]
M	0.0	NA	NA	NA	brain/spinal cord	astrocytoma	1/80
					Zymbal gland	carcinoma	3/80
					stomach	all tumors	0/80
					tongue	squamous cell tumors	1/75
M	3.42	24	high purity	drinking water	brain/spinal cord	astrocytoma	12/47 ($p<0.05$)
					Zymbal gland	carcinoma	4/47
					stomach	all tumors	3/46 ($p<0.05$)
					tongue	squamous cell tumors	2/7[e]
M	8.53	24	high purity	drinking water	brain/spinal cord	astrocytoma	22/48 ($p<0.05$)
					Zymbal gland	carcinoma	3/48
					stomach	all tumors	23/48 ($p<0.05$)
					tongue	squamous cell tumors	4/9[e] ($p<0.05$)
M	21.18	24	high purity	drinking water	brain/spinal cord	astrocytoma	30/48 ($p<0.05$)
					Zymbal gland	carcinoma	15/48
					stomach	all tumors	39/47 ($p<0.05$)
					tongue	squamous cell tumors	5/40[e] ($p<0.05$)
F	0.0	NA	NA	NA	brain/spinal cord	astrocytoma	0/80
					Zymbal gland	carcinoma	1/80
					stomach	all tumors	1/80
					tongue	squamous cell tumors	0/78
					mammary gland	malignant/benign	57/80
F	4.36	24	high purity	drinking water	brain/spinal cord	astrocytoma	17/48 ($p<0.05$)
					Zymbal gland	carcinoma	4/48
					stomach	all tumors	1/47
					tongue	squamous cell tumors	1/48
					mammary gland	malignant/benign	42/48 ($p<0.05$)

TABLE 5-2 (cont.)

Sex	Dose or Exposure (mg/kg/day)[b]	Duration of Treatment (months)	Purity of Compound[c]	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)[d]
F	10.76	24	high purity	drinking water	brain/spinal cord	astrocytoma	22/48 (p<0.05)
					Zymbal gland	carcinoma	6/48
					stomach	all tumors	12/48 (p<0.05)
					tongue	squamous cell tumors	1/5[e]
					mammary gland	malignant/benign	42/48 (p<0.05)
F	24.97	24	high purity	drinking water	brain/spinal cord	astrocytoma	24/48 (p<0.05)
					Zymbal gland	carcinoma	14/48 (p<0.05)
					stomach	all tumors	30/48 (p<0.05)
					tongue	all tumors	2/3[e] (p<0.05)
					mammary gland	malignant	35/48

QUALITY OF EVIDENCE

Strengths of Study:	The compound was administered for lifetime by a natural route to both sexes at three dose levels. Complete histologic examinations were performed. Tumors incidence appeared dose related in both sexes. Statisical analyses were performed.
Weakness of Study:	Animals in the two high dose groups had poor food and water consumption.
Overall Adequacy:	Adequate

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[a] Quest et al., 1980a; U.S. EPA, 1983a

[b] The dose was calculated from measured water consumption and body weight.

[c] The acrylonitrile was stablized with hydroquinone monoethyl ether (39 ppm).

[d] Tumor incidence expressed an number of rats bearing tumors/the number of rats examined microscopically for that particular organ.

[e] All samples were not taken from all animals

NA = Not applicable

and for female rats was 0.12, 0.36, 1.25, 3.65 and 10.89 mg/kg/day for animals ingesting water containing 1, 3, 10, 30 and 100 ppm of acrylonitrile, respectively. Interim sacrifices were performed at 6, 12 and 18 months, and the study terminated at 23 months for the female rats and 26 months for the male rats. In the third study (Bio/dynamics Inc., 1980c), Spartan rats (100 males and 100 females per group) received acrylonitrile in deionized water by gavage at 0.1 and 10.0 mg/kg/day, 5 days/week. The studies were terminated at 19 and 20 months Because of excessive mortality in the high-dose groups.

Histopathologic evaluation of the Bio/dynamics (1980a) study revealed an increased incidence of astrocytomas of the brain and spinal cord, carcinomas and adenomas of the Zymbal gland or ear canal and squamous cell carcinomas and papillomas of the forestomach in the high-dose males and females (Table 5-3). These tumors were primarily observed in dying animals, animals sacrificed when moribund or in animals sacrificed at intervals after the 12th month of study.

Histopathologic evaluation in the Bio/dynamics (1980b) study revealed an increased incidence of malignant tumor-bearing animals in the groups receiving 10, 30 and 100 ppm (Table 5-4). The observed tumors were astrocytomas of the CNS (brain or spinal cord) and squamous cell carcinomas of the ear canal as well as mammary gland carcinomas in the females receiving 100 ppm.

Histopathologic evaluation of the Bio/dynamics (1980c) study (Table 5-5) revealed increased incidences of tumors of the brain and ear canal (Zymbal gland) in high-dose males and females. Stomach tumors were observed only in high-dose males and mammary gland tumors were observed in high-dose females.

TABLE 5-3

Tumor Incidence in Spartan Rats Treated Orally with Acrylonitrile[a]

Sex	Dose or Exposure (mg/kg/day)[b]	Duration of Treatment (months)	Duration of Study (months)	Purity of Compound[c]	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)
M	0.0	NA	22	NA	NA	brain Zymbal gland stomach	astrocytoma carcinoma papilloma/carcinoma	2/98 1/100 3/98
M	0.093[a]	22	22	100%[b]	drinking water	brain Zymbal gland stomach	astrocytoma carcinomas papilloma/carcinoma	3/95 0/91 3/98
M	7.98[a]	22	22	100%[b]	drinking water	brain Zymbal gland stomach	astrocytoma carcinomas papilloma/carcinoma	23/97 ($p<0.05$) 14/93 ($p<0.05$) 12/97 ($p<0.05$)
F	0.0	NA	19	NA	NA	spinal cord brain Zymbal gland stomach	astrocytoma astrocytoma carcinomas papilloma/carcinoma	0/96 0/99 0/99 1/100
F	0.146[a]	19	19	100%[b]	drinking water	spinal cord brain Zymbal gland stomach	astrocytoma astrocytoma carcinomas papilloma/carcinoma	0/99 1/100 0/95 4/99
F	10.69[a]	19	19	100%[b]	drinking water	spinal cord brain Zymbal gland stomach	astrocytoma astrocytoma carcinomas papilloma/carcinoma	7/98 ($p<0.05$) 32/97 ($p<0.05$) 7/98 ($p<0.05$) 7/99 ($p<0.05$)

QUALITY OF EVIDENCE

Strengths of Study:	The compound was administered by a natural route for the lifespan of the animals to both sexes at 2 dose levels. The level of acrylonitrile in the drinking water was routinely monitored by GC. Extensive histopathology was performed.
Weakness of Study:	Early mortality required shortening the study from 24 months to 19-20 months.
Overall Adequacy:	Adequate

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[a] Bio/dynamics Inc., 1980a; U.S. EPA, 1983a

[b] The dose was calculated from measured water consumption and body weight.

[c] The authors reported that the acrylonitrile was "100% active ingredient."

NA = Not applicable

TABLE 5-4

Tumor Incidence in Fisher Rats Treated Orally with Acrylonitrile[a]

Sex	Dose or Exposure (mg/kg/day)[b]	Duration of Treatment (months)	Duration of Study (months)	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)
M	0.0	NA	26	NA	NA	brain ear canal stomach spinal cord	astrocytoma carcinoma/adenoma all tumors astrocytoma	2/200 2/89 0/199 1/196
M	0.08	26	26	100%	drinking water	brain ear canal stomach spinal cord	astrocytoma carcinoma/adenoma all tumors astrocytoma	2/100 1/97 1/100 0/99
M	0.25	26	26	100%	drinking water	brain ear canal stomach spinal cord	astrocytoma carcinoma/adenoma all tumors astrocytoma	1/100 0/93 4/97 ($p<0.05$) 0/92
M	0.84	26	26	100%	drinking water	brain ear canal stomach spinal cord	astrocytoma carcinoma/adenoma all tumors astrocytoma	2/100 2/88 4/100 ($p<0.05$) 0/98
M	2.49	26	26	100%	drinking water	brain ear canal stomach spinal cord	astrocytoma carcinoma/adenoma all tumors astrocytoma	10/99 ($p<0.05$) 7/94 ($p<0.05$) 4/100 ($p<0.05$) 0/99
M	8.37	26	26	100%	drinking water	brain ear canal stomach spinal cord	astrocytoma carcinoma/adenoma all tumors astrocytoma	21/99 16/93 1/100 4/93
F	0.0	NA	23	NA	NA	brain ear canal stomach spinal cord	astrocytoma carcinoma/adenoma all tumors astrocytoma	1/199 0/193 1/99 1/197
F	0.12	23	23	100%	drinking water	brain ear canal stomach spinal cord	astrocytoma carcinoma/adenoma all tumors astrocytoma	1/100 0/94 1/100 0/97

TABLE 5-4 (cont.)

Sex	Dose or Exposure (mg/kg/day)[b]	Duration of Treatment (months)	Duration of Study (months)	Purity of Compound[c]	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)
F	0.36	23	23	100%	drinking water	brain	astrocytoma	2/101
						ear canal	carcinoma/adenoma	2/92
						stomach	all tumors	2/100
						spinal cord	astrocytoma	0/99
F	1.25	23	23	100%	drinking water	brain	astrocytoma	4/95 ($p<0.05$)
						ear canal	carcinoma/adenoma	4/90
						stomach	all tumors	2/97
						spinal cord	astrocytoma	1/92 ($p<0.05$)
F	3.65	23	23	100%	drinking water	brain	astrocytoma	6/100 ($p<0.05$)
						ear canal	carcinoma/adenoma	5/94 ($p<0.05$)
						stomach	all tumors	4/100 ($p<0.05$)
						spinal cord	astrocytoma	0/96
F	10.89	23	23	100%	drinking water	brain	astrocytoma	23/98 ($p<0.05$)
						ear canal	carcinoma/adenoma	10/86 ($p<0.05$)
						stomach	all tumors	2/97
						spinal cord	astrocytoma	1/91

QUALITY OF EVIDENCE

Strengths of Study:	The compound was administered for an appreciable portion of the animals' lifespan by a natural route to both sexes at 5 dose levels.
Overall Adequacy:	Adequate

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[a] Bio/dynamics Inc., 1980b; U.S. EPA, 1983a

[b] The dose was calculated from measured water consumption and body weight.

[c] The authors reported that the acrylonitrile was "100% active ingredient".

NA = Not applicable

TABLE 5-5

Tumor Incidence in Spartan Rats Treated by Gavage with Acrylonitrile[a]

Sex	Dose or Exposure (mg/kg/day)	Duration of Treatment (months)	Duration of Study (months)	Purity of Compound[b]	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)
M	0.0	NA	19-20	NA	NA	brain Zymbal gland stomach	astrocytoma carcinoma carcinoma/papilloma	2/100 1/96 2/99
M	0.1	19-20	19-20	100%	water	brain Zymbal gland stomach	astrocytoma carcinoma carcinoma/papilloma	0/97 0/93 6/97
M	10	19-20	19-20	100%[a]	water	brain Zymbal gland stomach	astrocytoma carcinoma carcinoma/papilloma	16/98 ($p<0.05$) 10/96 ($p<0.05$) 40/99 ($p<0.05$)
F	0.0	NA	19-20	NA	NA	brain Zymbal gland stomach mammary gland	astrocytoma carcinoma carcinoma/papilloma carcinoma	1/99 0/85 2/99 7/101
F	0.1	19-20	19-20	100%[a]	water	brain Zymbal gland stomach mammary gland	astrocytoma carcinoma carcinoma/papilloma carcinoma	2/100 0/94 4/99 6/100
F	10	19-20	19-20	100%[a]	water	brain Zymbal gland stomach mammary gland	astrocytoma carcinoma carcinoma/papilloma carcinoma	17/100 ($p<0.05$) 9/94 ($p<0.05$) 17/99 ($p<0.05$) 22/101 ($p<0.05$)

QUALITY OF EVIDENCE

Strengths of Study:	The compound was administered for an appreciable portion of the animals' lifespan. The group size was large. Extensive histology was performed.
Weakness of Study:	The compound was administered by gavage, allowing transient high levels in the body. Early mortality required shortening the study from 24 months to 19-20 months.
Overall Adequacy:	Adequate

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[a] Bio/dynamics Inc., 1980e

[b] The authors reported that the acrylonitrile was "100% active ingredient".

NA - Not applicable

Maltoni et al. (1977) treated groups of 40 male and 40 female Sprague-Dawley rats by gavage with acrylonitrile in olive oil at 0 and 5 mg/kg/day, 3 days/week for 52 weeks. Although the use of a single dose level and the short duration limit the adequacy of this study, additional evidence of carcinogenicity is provided, as evidenced by a moderate increase in mammary gland and forestomach tumors in female rats.

In a multigeneration study described more fully in Section 5.4, rats were maintained on drinking water containing 100 and 500 ppm acrylonitrile (Beliles et al., 1980). Rats of the F_1 generation at the high-dose level had statistically significantly increased incidences of astrocytomas ($p=0.036$) and Zymbal gland tumors ($p=0.036$) compared with controls, providing further evidence of a carcinogenic effect of acrylonitrile.

A second study performed by Dow Chemical Company involved a 2-year inhalation exposure of rats to the vapors of acrylonitrile (Quast et al., 1980b). Three groups of Sprague-Dawley rats, consisting of 100 male and 100 female animals, were exposed to acrylonitrile at concentrations of 0, 20 and 80 ppm. The exposure was for 6 hours/day, 5 days/week for a period of 2 years. The animals were killed at the end of the 2 years or when moribund, and were subjected to gross pathologic examination. From the animals in the 0 and 80 ppm group, comprehensive sets of tissue were obtained for histologic examination, while for most of the 20 ppm group (80%), 23 selected tissues were examined histologically. The cumulative mortality data are shown in Tables 5-6 and 5-7.

Microscopic examination of tissues revealed a treatment-related statistically significant incidence of tumors in the CNS, Zymbal gland (ear canal), tongue, small intestine and mammary gland. In male and female rats, statistically significant increased incidences were observed only at the 80

TABLE 5-6

Cumulative Mortality Data of Male Rats Exposed by Inhalation for 2 Years to Acrylonitrile[a,b]

Days on Test	Exposure Concentration		
	0 ppm	20 ppm	80 ppm
0-30	0	1	0
31-60	0	1	0
61-90	0	1	1
91-120	0	2	1
121-150	1	2	1
151-180	2	3	2
181-210	2	3	6
211-240	2	4	12[c]
241-270	2	5	13[c]
271-300	2	5	14[c]
301-330	3	6	16[c]
331-360	3	6	18[c]
361-390	4	8	19[c]
391-420	6	9	22[c]
421-450	11	12	24[c]
451-480	14	15	28[c]
481-510	19	26	39[c]
511-540	23	34	47[c]
541-570	27	38	56[c]
571-600	35	47	63[c]
601-630	43	59[c]	76[c]
631-660	62	68	83[c]
661-690	71	72	85[c]
691-720	78	81	94[c]
721-735	82	86	96[c]
Total Number of rats	100	100	100

[a] Source: Quast et al., 1980b

[b] Data listed as number dead, which is equal to percent dead

[c] Significantly different from controls by Fisher's Exact Probability Test, $p < 0.05$.

TABLE 5-7

Cumulative Mortality Data of Female Rats Exposed by Inhalation for 2 Years to Acrylonitrile Vapors[a,b]

Days on Test	Exposure Concentration 0 ppm	 20 ppm	 80 ppm
0-30	1	0	0
31-60	1	0	0
61-90	1	0	0
91-120	1	0	0
121-150	1	0	0
151-180	1	0	0
181-210	1	1	1
211-240	1	1	2
241-270	3	1	4
271-300	5	1	6
301-330	5	2	9
331-360	7	2	11
361-390	9	3	19[c]
391-420	11	5	27[c]
421-450	14	10	33[c]
451-480	14	14	41[c]
481-510	19	22	57[c]
511-540	26	31	71[c]
541-570	34	36	80[c]
571-600	36	43	88[c]
601-630	50	54	94[c]
631-660	63	70	98[c]
661-690	66	81[c]	98[c]
691-720	71	88[c]	99[c]
721-735	78	91[c]	99[c]
Total Number of rats	100	100	100

[a] Source: Quast et al., 1980b

[b] Data listed as number dead, which is equal to percent dead

[c] Significantly different from controls by Fisher's Exact Probability Test, $p < 0.05$.

ppm dose levels except for glial cell tumors of the CNS, which were also increased in female rats at 20 ppm. Detailed results are presented in Table 5-8.

Maltoni et al. (1977) exposed Sprague-Dawley rats to atmospheres containing 5, 10, 20 and 40 ppm acrylonitrile 4 hours/day, 5 days/week for 12 months. The rats were maintained for their lifetime and histological examinations of selected tissues were performed. The incidence of total tumors is shown in Table 5-9. Slight increases were observed in mammary gland tumors of males and females, the forestomach of males and the skin of females. Maltoni et al. (1977) stated that these results indicated a "borderline carcinogenic effect." The sensitivity of the assay was low because of the low concentration of acrylonitrile used and the short exposure period.

There are no community epidemiologic studies available that attempt to demonstrate an association between exposure to ambient levels of acrylonitrile and the development of cancer; however, an occupational epidemiologic study that involved workers exposed to acrylonitrile at a DuPont textile fibers plant in Camden, South Carolina was conducted by O'Berg (1980). The study cohort consisted of 1345 male employees who had potential exposure to acrylonitrile at some time between start-up of the plant in 1950 and 1966. The cut-off date allowed for a minimum 10-year follow-up through the end of 1976. As discussed by U.S. EPA (1983a), the levels of exposure were designated as high (20 ppm), medium (10 ppm) and low (5 ppm).

Overall, 25 cases of cancer occurred, with 20.5 expected based on company rates and 25.5 based on national rates. Of the 25 cases occurring, 8 were respiratory cancer cases compared with 4.4 expected cases based on company rates and 6.1 expected based on national rates. Excesses were found

TABLE 5-8

Treatment Related Differences of Tumor Incidence in Male and Female Sprague-Dawley Rats Exposed by Inhalation to Acrylonitrile

Sex	Dose or Exposure (months)	Duration of Treatment (months)	Duration of Study	Purity of Compound[b]	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence[c] (p value)
M	0.0 ppm	NA	24 months	NA	NA	brain/spinal cord	glial cell tumors	0/100
						tongue	all tumors	1/96
						small intestine	benign and malignant	2/99
						Zymbal gland	benign and malignant	2/100
M	20 ppm, 6 hours/ day, 5 days/week	24	24	high purity	in air	brain/spinal cord	glial cell tumors	4/99
						tongue	all tumors	0/14
						small intestine	benign and malignant	2/20
						Zymbal gland	benign and malignant	4/100
M	80 ppm, 6 hours/ day, 5 days/week	24	24	high purity	in air	brain/spinal cord	glial cell tumors	22/99 ($p<0.05$)
						tongue	all tumors	7/89 ($p<0.05$)
						small intestine	benign and malignant	15/98 ($p<0.05$)
						Zymbal gland	benign and malignant	11/100 ($p<0.05$)
F	0.0 ppm	NA	24	NA	NA	brain/spinal cord	glial cell tumors	0/100
						Zymbal gland	benign and malignant	0/100
						mammary gland	adenocarcinoma	9/100
F	20 ppm, 6 hours/ day, 5 days/week	24	24	high purity	in air	brain/spinal cord	glial cell	8/100 ($p<0.05$)
						Zymbal gland	benign and malignant	1/100
						mammary gland	adenocarcinoma	8/100

TABLE 5-8 (cont.)

Sex	Dose or Exposure	Duration of Treatment (months)	Duration of Study (months)	Purity of Compound[b]	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence[c] (p value)
F	80 ppm, 6 hours/ day, 5 days/week	24	24	high purity	in air	brain/spinal cord Zymbal gland mammary gland	glial cell benign and malignant adenocarcinoma	21/100 ($p<0.05$) 11/100 ($p<0.05$) 20/100 ($p<0.05$)

QUALITY OF EVIDENCE

Strengths of Study:	Compound administered by a relevant route for the lifespan of the animals to both sexes at 2 concentrations. Extensive histology was performed. The concentration was determined by GC 2-4 times during each exposure. Statiscal analyses were performed.
Overall Adequacy:	Adequate

[a] Quast et al., 1980b; U.S. EPA, 1983a

[b] The acrylonitrile contained the inhibitor hydroquinone monomethyl ether.

[c] The tumor incidence is expressed as tumors per number of animals examined.

NA = Not applicable

TABLE 5-9

Incidence of Total Tumors of Male and Female Sprague-Dawley Rats Maintained for Lifetime while being Exposed by Inhalation to Various Dose Levels of Acrylonitrile*

Sex	Dose or Exposure (months)	Duration of Treatment	Vehicle or Physical State	Tumor Incidence
M	0.0 ppm	NA	NA	4/30
M	5 ppm, 4 hours/day, 5 days/week	12	in air	1/30
M	10 ppm, 4 hours/day, 5 days/week	12	in air	10/30
M	20 ppm, 4 hours/day, 5 days/week	12	in air	13/30
M	40 ppm, 4 hours/day, 5 days/week	12	in air	12/30
F	0.0 ppm, 4 hours/day, 5 days/week	NA	NA	9/30
F	5 ppm, 4 hours/day, 5 days/week	12	in air	17/30
F	10 ppm, 4 hours/day, 5 days/week	12	in air	11/30
F	20 ppm, 4 hours/day, 5 days/week	12	in air	14/30

TABLE 5-9 (cont.)

Sex	Dose or Exposure	Duration of Treatment (months)	Vehicle or Physical State	Tumor Incidence
F	40 ppm, 4 hours/day, 5 days/week	12	in air	8/30

QUALITY OF EVIDENCE

Strengths of Study:	Compound was administered to both sexes at 4 concentrations by a relevant route for the lifespan of the animals.
Weakness of Study:	The duration of exposure was short. The concentrations tested were all below the maximal tolerated concentrations.
Overall Adequacy:	Limited
Comments:	The author claimed that these results indicated only "a border-line oncogenic effect."

*Maltoni et al., 1977

NA = Not applicable; NR = not reported

among hourly employees who had worked during the 1950-1952 plant start-up (8 cases vs. 2.6 expected, $p<0.01$). A trend toward increased risk was seen with increased duration and higher levels of exposure. During the follow-up period 1970-1976, there were six cases vs. 1.5 expected ($p<0.01$). Total cancers for this group were 17 vs. 5.6 effected ($p<0.01$).

In workers with moderate exposure and probable latent periods of $\geq$15 years, the observed and expected numbers of cancer cases were 13 and 5.5, respectively. Half of this excess was due to respiratory cancer, 5 vs. 1.4 effected ($p<0.05$). As discussed by U.S. EPA (1983a), adjustment for the effects of smoking resulted in 5 observed vs. 1.6 expected ($p<0.05$). Therefore the relative risk is $5.0/1.6 = 3.1$.

Other epidemologic studies have been discussed in U.S. EPA (1983a). Because of many limitations and biases, the studies were inconclusive and could not be used to support or refute whether or not acrylonitrile was carcinogenic in humans.

5.2. MUTAGENICITY

The results of mutagenicity testing on acrylonitrile are summarized in Table 5-10 and discussed briefly below.

Several investigators (De Meester et al., 1978; Lijinsky and Andrews, 1980; Florin et al., 1980; Venitt et al., 1977; Poncelet et al., 1980) reported that acrylonitrile was not mutagenic in *Salmonella typhimurium* when tested in the "classical" plate incorporation assay. Acrylonitrile was found to be mutagenic in *S. typhimurium* in the presence of metabolic activation (DeMeester et al., 1978, 1979; Milvy and Wolff, 1977; Poncelet et al., 1980; Duverger-Van Bogaert et al., 1981; Cerna et al., 1981).

In solution, acrylonitrile produced reverse mutations in a plate incorporation assay using *Escherichia coli* WP2, WP2 uvrA and WP2 uvrApolA without

TABLE 5-10

Mutagenicity Testing of Acrylonitrile

Assay	Indicator/ Organism	Purity	Applicator	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation	*Salmonella typhimurium* TA1535, 1537, 1538, 98, 100 *S. cerevisiae* D4	NR	plate incorporation	up to 500 µℓ/ plate	± S-9	–	negative with possible exception of a slight positive response in *S. cerevisiae* D4	Litton Bionetics, Inc. 1976
Reverse mutation	*S. typhimurium* TA98, TA100, TA1530, TA1535, TA1950 and TA1978	99%	plate incorporation, fluctuation vapor exposure	0.2% vapor	± S-9	–, ±, ±	acrylonitrile was mutagenic in strain TA1530 in the presence of S-9 by bacterial fluctuation test, and mutagenic in strains TA1530, TA1535 and TA1950 in the presence of S-9 in an atmosphere of 0.2% gaseous exposure; negative results in plate incorporation method	De Meester et al., 1978
Reverse mutation	*S. typhimurium* TA1530	99%	liquid suspension	70 µmol/mℓ	± S-9	±	NC	Duverger-Van Bogaert et al. 1981
Reverse mutation	*S. typhimurium* TA100, TA1535	99%	NR	0.014-14 mM	± S-9	±	NC	Cerna et al., 1981
Reverse mutation	*S. typhimurium* 5 strains	NR	liquid suspension or plate incorporation	NR	± S-9	+	mutagenic in ≥1 strains but strains not reported; not indicated if results were reported in presence or absence of S-9	Lijinsky and Andrews,1980
Reverse mutation	*S. typhimurium* TA1530, TA1538	99%	fluctuation	0.2% in the atmosphere	± S-9	±	the reverse rate increased when S-9 fraction was obtained from mice; pretreatment of mice with phenobarbital enhanced S-9 mediated mutagenicity of acrylonitrile	De Meester et al., 1979

TABLE 5-10 (cont.)

Assay	Indicator/ Organism	Purity	Applicator	Concentration or Dose	Activating System	Response	Comment	Reference
Chromosome aberrations	NMRI male mice bone marrow	NR	mice given single i.p. injection	20 or 30 mg/kg	NA	-	aberrations scored were gaps, breaks and rearrangements	Leonard et al., 1981
Dominant lethal assay	NMRI male mice	NR	i.p.	30 mg/kg	NA	-	results considered inconclusive because background control frequency was very high (33.6% postimplantation loss)	Leonard et al., 1981
Chromosome aberrations	Albino Swiss mice, Sprague-Dawley rats bone marrow	99.5%	oral or i.p.	mice-7,14 and 21 mg/kg oral or 10,15,20 mg/kg(i.p.) for 4,15 or 30 days. Rats - 40 mg/kg/day for 16 days	NA	-	aberrations scored were gaps, isogaps, breaks, fragments and translocations	Rabello-Gay and Ahmed, 1980
Chromosome aberrations	human lymphocytes	NR	occupational exposure	5 ppm from 1963-1974 and 1.5 ppm from 1975-1977	NA	-	cohort exposed to acrylonitrile for 15.3 years; aberrations scored were gaps and isogaps; other aberrations scored were not defined	Thiess and Fleig, 1978
Single strand DNA breaks	Syrian Golden hamster cells	99%	cell culture	50,100,200 and 400 µg/mℓ	none	+	DNA breakage at 200 and 400 µg/mℓ but not at 50 or 100 µg/mℓ, toxicity data not given; results could be due to nonspecific toxicity	Parent and Casto, 1979
Chromosomal aberrations; dominant lethal	mice bone marrow,spermatogonia	NR	inhalation	20 and 100 mg/m³	NA	-	negative in both tests	Zhurkov, et al., 1983

TABLE 5-10 (cont.)

Assay	Indicator/ Organism	Compound and/or Purity	Applicator	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation	S. typhimurium TA98, TA100, TA1535, TA1537	NR	plate incorporation	3 μmol/plate	± S-9	−	NC	Florin et al., 1980
Reverse mutation	S. typhimurium Escherchia coli	NR	gradient plate test	0.1-1 μg/mℓ 1-10 μg/mℓ 10-100 μg/mℓ 100-1000 μg/mℓ	± S-9	+	positive, but authors did not indicate if mutagenic activity was dependent on metabolic activation	McMahon et al., 1979
Reverse mutation	S. typhimurium E. coli WP2	99%	plate incorporation, fluctuation	10,75,150 μmol/ plate. $4x10^{-4}$ to $2x10^{-4}$ M for fluctuation	± S-9	− ±	negative for S. typhimurium, weakly positive in absence of S-9 for E. coli	Venitt et al., 1977
Reverse mutation	S. typhimurium TA1535 TA1538 TA1978	99%	spot test, liquid suspension and vapor	spot test: 5 and 10 μℓ, liquid suspension: 5,10, 50μℓ for 30 minutes-4 hours	± S-9	+	negative results for spot test; weakly positive in the presence of metabolic activation with liquid suspension and vapor	Milvy and Wolff, 1977
Urinalysis	S. typhimurium TA1530	99%	plate incorporation	30 mg/kg	± S-9	+	positive in the absence of metabolic activation. Mutagenic activity in rat urine was reduced when animals were pretreated by pyrazole and suppressed after pretreatment by $CoCl_2$, SKF525A, and trichloroacetonitrile	Lambotte-Vandepaer et al., 1980, 1981
Reverse mutation	S. typhimurium TA1530 TA1535	99%	plate incorporation, fluctuation, vapor exposure	dilutions of 10 μmol/plate; 0.2% gaseous exposure	± S-9	+	mutagenic in TA1530 in the presence of S-9 by bacterial fluctuation test, positive in 0.2% gaseous atmosphere, negative for plate incorporation	Poncelet et al., 1980
Sex-linked recessive lethal test	Drosophila melanogaster	NR	injection of 0.1% solution intraabdomen	0.1%	NA	+	results suggestive of 3-fold increase in mutation frequency. Toxicity not given. No concurrent positive controls and information concerning negative controls not given	Benes and Sram, 1969

TABLE 5-10 (cont.)

Assay	Indicator/ Organism	Purity	Applicator	Concentration or Dose	Activating System	Response	Comment	Reference
Sister chromatid exchange and unscheduled DNA synthesis	human lymphocytes	99%	cell culture	$5x10^{-3}$ to $5x10^{-6}$ M	± S-9	±	In the presence of S-9 and at a concentration of $5x10^{-4}$ M, a significant increase in the sister chromatid exchange frequency was observed; unscheduled DNA synthesis increased at $5x10^{-3}$ M	Perocco et al., 1982
Chromosomal aberrations	rat bone marrow	NR	drinking water	35,210 or 500 ppm	NA	-	negative	Litton Bionetics, Inc. 1976
Forward mutation	mouse lymphoma L5178x	NR	cell culture	0.1-0.0005%	± S-9	-	negative	Litton Bionetics, Inc. 1976

NR - Not Reported; NA - not applicable

a metabolic activation system. Acrylonitrile was also mutagenic in the fluctuation test in E. coli WP2 and WP2 uvrApolA at a concentration 20- to 40-fold less than that used in the plate assay (Venitt et al., 1977).

Results of several in vitro experiments demonstrated that the cytochrome P450 system plays a key role in the activation of acrylonitrile (Ahmed and Abreu, 1982; Lambotte-Vandepaer et al., 1981; Duverger-Van Bogaert et al., 1981). Guengerich et al. (1981) reported that in vitro a reconstituted cytochrome P450 system catalyzed the oxidation of acrylonitrile to 2-cyanoethylene-oxide (glycidenitrile). This epoxide can bind irreversibly to nucleic acids as well as proteins (Guengerich et al., 1981) and has been shown to be directly mutagenic toward S. typhimurium (Cerna et al., 1981). 2-Cyanoethylene-oxide also induced strand breaks in SV40 phage DNA (Peter et al., 1983). Results of several metabolic studies indicate that this epoxide is also formed in vivo; presence of several metabolites in the urine of acrylonitrile-pretreated rats could be explained by spontaneous rearrangement of the intermediate epoxide (Langvardt et al., 1980; Lambotte-Vandepaer, 1981). Geiger et al. (1983) examined acrylonitrile metabolism in isolated rat hepatocytes and estimated that at low concentrations of acrylonitrile the major mode of metabolism involves conjugation of acrylonitrile with glutathione. In their experiment, 10% of the acrylonitrile was oxidatively metabolized to 2-cyano-ethylene-oxide.

The ability of acrylonitrile to induce chromosomal aberrations in vivo has been investigated in both rats and mice. Several investigators have reported no significant increases in the incidence of chromosomal aberrations (gaps, breaks, fragments, Robertsonian translocations) in mouse bone marrow cells (Leonard et al., 1981; Rabello-Gay and Ahmed, 1980; Zhurkov et al., 1983). Leonard et al. (1981) and Zhurkov et al. (1983) also conducted a dominant lethal assay in mice. No differences in the postimplantation loss between the control and acrylonitrile-treated groups were observed.

Thiess and Fleig (1978) examined the clastogenic effects in lymphocytes of 18 workers who were exposed to acrylonitrile for an average of 15.3 years. One hundred cells were analyzed per person. Chromosomal aberrations in the exposed group were $1.8\pm1.3\%$ (excluding gaps) and $5.5\pm2.5\%$ (including gaps and isogaps), while chromosome aberrations in the control group were $2.0\pm1.6\%$ (excluding gaps) and $5.1\pm2.4\%$ (including gaps and isogaps). Therefore, no apparent chromosomal damage was detected in these workers.

Perocco et al. (1982) reported a significant increase in the sister chromatid exchange frequency in human lymphocytes in the presence of metabolic activation and exposed to a concentration of $5\text{x}10^{-4}$ M acrylonitrile. Unscheduled DNA synthesis also increased at $5\text{x}10^{-2}$ M acrylonitrile.

Parent and Casto (1979) reported that acrylonitrile caused single strand DNA breaks in primary Syrian golden hamster embryo cells *in vitro* as detected by alkaline sucrose gradient sedimentation. When cells were treated for 18 hours at acrylonitrile doses of 200 or 400 µg/mℓ, a shift in sedimentation patterns was observed; this shift did not occur at 50 or 100 µg/mℓ. The authors suggested that these shifts are comparable to those produced by known carcinogens and are not seen with noncarcinogenic chemicals.

5.3. TERATOGENICITY

The teratogenicity of acrylonitrile has been investigated using Sprague-Dawley rats exposed to the compound by inhalation or by gavage on days 6-15 of gestation (the results of both the inhalation and gavage treatments were reported by Murray et al., 1978, while a detailed report of the results of the gavage treatment was presented by Murray et al., 1976). Acrylonitrile was administered at doses of 10, 25, and 65 mg/kg/day per os or by exposing the animals to an atmosphere of 40 or 80 ppm (87 or 174 mg/m^3) acrylonitrile for 6 hours/day. By measuring blood levels of acrylonitrile and its metabolites, an exposure to 80 ppm (174 mg/m^3) acrylonitrile for 6 hours was estimated to be equivalent to a single 23 mg/kg dose of acrylonitrile. On day 21 of gestation, the dams were sacrificed and examined for implants and fetal abnormalities.

Rats treated orally at 65 mg/kg/day showed moderate signs of toxicity with decreased body weight, thickening of the nonglandular portion of the stomach and increased liver weight. The only adverse effect on animals treated at 25 mg/kg/day was a slight thickening of the nonglandular portion of the stomach, while animals given the lowest dose or animals exposed by inhalation showed no major treatment-related toxic effects. In all cases, except the animals treated with 10 mg/kg/day, food consumption declined initially during the first 3-day interval following treatment, but returned to normal during the two subsequent 3-day intervals. Neither the stress on the dams from the mild toxic effects of acrylonitrile nor any direct toxic effects of acrylonitrile on the fetus significantly altered the number of litters, implants per dam or live fetuses per litter. A slight but significant decrease in fetal body weight and crown-rump length was noted in the 65 mg/kg/day group, but not in any of the other groups.

Fetal malformations were observed primarily in the offspring of animals that received acrylonitrile by gavage (Table 5-11). Following inhalation of acrylonitrile, there was no significant single major malformation observed; however, when malformations were considered collectively, there was a

TABLE 5-11

Incidence of Fetal Malformations Among Litters of Rats Given Acrylonitrile[a]

Type of Malformation	Acrylonitrile Given by Gavage (mg/kg bw)				Acrylonitrile Given by Inhalation (ppm)		
	0	10	25	65	0	40	80
	No. fetuses/No. litters examined						
External and skeletal malformations	443/38	388/35	312/29	212/17	421/33	441/33	406/35
Visceral malformations	154/38	135/35	111/29	71/17	140/33	148/36	136/35
	No. of fetuses (litters) affected						
External malformations							
Short tail	1 (1)	0 (0)	2 (2)	8 (6)[b]	0 (0)	0 (0)	2 (2)
Short trunk[c]	0 (0)	0 (0)	0 (0)	3 (3)[b]	0 (0)	0 (0)	1 (1)
Imperforate anus[c]	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)
Omphalocele	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)
Visceral malformations							
Right-sided aortic arch	0 (0)	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Missing kidney, unilateral	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Anteriorly-displaced ovaries[c]	0 (0)	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	1 (1)
Skeletal malformations							
Missing vertebrae (associated with short tail)[c]	1 (1)	0 (0)	2 (2)	8 (6)[b]	0 (0)	0 (0)	2 (2)
Missing two vertebrae and a pair of ribs	7 (1)	0 (0)	7 (2)	0 (0)	8 (1)	2 (1)	7 (2)
Hemivertebra	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Total malformed	8 (2)	0 (0)	10 (4)	8 (6)[b]	8 (1)	3 (2)	11 (6)[d]

[a] Source: Murray et al., 1978

[b] Values differ significantly from the control value ($p<0.05$) using the Wilcoxon test as modified by Haseman and Hoel (1974).

[c] This malformation was observed only in fetuses with short tail.

[d] Value differs significantly from the control value ($p=0.06$) using the Wilcoxon test as modified by Haseman and Hoel (1974).

significant (p=0.06) but slight increase in the 80 ppm (174 mg/m³) exposure group. At the high dose level in the gavage-treated animals, there was a significant increase in acaudate or short-tailed fetuses. The majority of other abnormalities including short trunk, anteriorly displaced ovaries, missing ribs and imperforate anus were observed in the acaudate and short-tailed fetuses whether these animals were from the control or treated groups. The only anomaly that occurred solely in treated animals was a right-sided aorticarch, which appeared in one fetus from the 25 mg/kg/day group and one fetus from the 65 mg/kg/day group. This anomaly had never been noted in >1000 litters examined by this laboratory.

The authors concluded that the malformations that occurred in the 65 mg/kg/day group were caused by effects of acrylonitrile directly on the fetus and not by effects on the dam. This conclusion was based on historical data indicating that mild stress, as caused by acrylonitrile treatment, did not lead to these types of malformations and on the lack of correlation between gross signs of toxicity in the dams (e.g., poor weight gain and decrease in food consumption) and litters with malformed fetuses. There also appeared to be a dose response relationship because the 25 mg/kg/day group and the 80 ppm (174 mg/m³) exposure group also showed increased incidences of malformed fetuses; however, since these increases were not statistically significant when compared with control animals, this can only be suggestive evidence.

Intraperitoneal injection of acrylonitrile at 1.51-2.26 mmol/kg (80-120 mg/kg) on day 8 of gestation in Golden hamsters induced exencephaly, encephaloceles, rib fusions and bifurcations in the offspring and resulted in toxicity to the dams (Willhite, et al., 1981). Multiple i.p. injections of sodium thiosulfate at 4.03 mmol/kg (1 g/kg) protected both dams and embryos against toxicity. When the larger dose of acrylonitrile was given in the presence of sodium thiosulfate, teratogenic effects were observed in the absence of maternal poisoning. Scheufler (1980) reported that a single i.p. injection of 32 mg/kg acrylonitrile on day 5 or 7 of pregnancy increased the postimplantation mortality of mice embryos 3- to 7-fold. Daily injections of 26 mg/kg during days 1-14 or 7-14 of pregnancy did not increase the embryo mortality.

5.4. OTHER REPRODUCTIVE EFFECTS

Belliles et al. (1980) performed an extensive 3-generation reproductive study on Charles River rats that were treated with 100 or 500 ppm acrylonitrile in drinking water. The rats were initially exposed following weaning, and mated 100 days after the start of the experiment. Two litters were produced from each female and members of the second litter were used to produce the next generation (rats from the first litter were used only when an insufficient number of pups was available from the second litter). The parents of the first generation showed some adverse effects of treatment in the 500 ppm group, with food and water consumption and body weights significantly lower than those of control animals (other generations were not monitored for these parameters). Reproductive toxicity was observed in the two matings of the first generation, with an increased number of deaths during the lactation period among pups of animals that had been treated at the 500 ppm level. These deaths may have been a result of acrylonitrile's effect on the dams, since pups fostered by untreated dams had normal survival. In the other generations, reproductive capacity and pup survival were within the normal range. The only adverse effect observed in pups that survived treatment was a decrease in body weight in the 500 ppm group.

Poor weight gain in the pups may have been caused by poor lactation in the dams that was due to the decreased water consumption. Ten weanlings of each sex from the control and high-dose groups of the F_{3b} litter were sacrificed for comprehensive histopathological evaluation. No adverse findings were noted in tissues taken routinely for histologic evaluation. Acrylonitrile appeared to have little direct effect on the development of the embryo and pup up to the time of weaning.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

Studies have been conducted in which animals were exposed repeatedly to acrylonitrile, although the duration of exposure was less than chronic. These studies provided information on the sublethal effects of acrylonitrile and indicate possible target organs involved in the chronic toxicity of this compound.

In a preliminary study, Dudley et al. (1942) exposed four rhesus monkeys and two dogs to an atmosphere containing 56 ppm (122 mg/m³) acrylonitrile for 4 hours/day, 5 days/week, over a 4-week period. The rhesus monkeys showed no overt signs of toxicity. Of the two dogs treated, one died during the first exposure period and the second had intermittent paralysis of the hind legs following three of the exposure periods (the 5th, 13th, and 14th). In subsequent experiments, 16 rats, 16 guinea pigs, 3 rabbits and 4 cats were exposed to 100 ppm (217 mg/m³) acrylonitrile, and 16 rats, 16 guinea pigs, 4 rabbits, 4 cats and 2 rhesus monkeys were exposed to 153 ppm (332 mg/m³) acrylonitrile. The exposure conditions were similar to those described previously except the period was increased to 8 weeks. At the 100 ppm (217 mg/m³) level, rats and guinea pigs showed only slight lethargy. Three female rats gave birth to normal pups during the study. The rabbits did not gain weight during the experiment and the cats suffered the most severe symptoms of vomiting and loss of weight. At the highest exposure level severe toxicity was noted in all animals, with many dying before completion of the study.

Dudley et al. (1942) examined the spleen, kidneys, liver, lungs, heart, pancreas, lymph nodes, stomach and small and large intestines of 18 rats, 6 rabbits, 6 cats, 16 guinea pigs and 1 monkey for pathological changes (there was no explanation of how the animals were selected for examination). The spleen of rats showed hemosiderosis, which is indicative of blood destruction. The kidneys of most animals showed renal irritation, with hyaline casts in animals in the two higher exposure groups (the exceptions were 1 cat and 1 rabbit exposed at the 100 ppm level and 1 monkey exposed at the 153 ppm level). Interstitial nephritis, although not very extensive, was also noted in many animals (the exception being the monkey and rats exposed at the 100 ppm level). Subacute bronchopneumonia was present in at least some members of all the species studied except the cat; the pneumonia appeared as congestion and edema in the alveoli. Cats were the only species that showed signs of liver damage, although the exact lesions were not described.

Hematological determinations in rats and rabbits were made by Dudley et al. (1942) using animals that had been exposed to 153 ppm (332 mg/m^3) acrylonitrile. These determinations revealed no changes in red and white blood cell counts or hemoglobin levels. At the end of the 1st week of exposure, an increase in eosinophils was noted using differential cell counts, with the maximum for rabbits and rats being 42 and 21% above control, respectively. Minami et al. (1973) claimed that changes in the partial pressures of oxygen and carbon dioxide in the blood occurred, along with increases in hemoglobin and hematocrit values following exposure of eight rabbits once per week for 8 hours to 20 ppm (43 mg/m³) acrylonitrile for a period of 8 weeks. Because of the small differences observed and the relatively large standard deviations, however, the statistical significance of these conclusions is Questionable.

Knobloch et al. (1972) observed changes in the peripheral blood pattern and functional disorders in the respiratory, casdiovascular and renal systems as well as signs of neuron lesion in the CNS in rats and rabbits inhaling 50 mg/m³ acrylonitrile for 6 months. Babanov et al. (1972) exposed rats (number, species and sex not reported) to 0.495 mg/m³ acrylonitrile vapor, 5 hours/day, 6 days/week, for 6 months. The rats developed CNS disorders, increased erythrocyte count, decreased leukocyte count, increased total protein catalase and peroxidase content, decreased ascorbic acid content of blood and an increased number of free sulfhydryl groups in the liver and blood serum.

In an abstract, Szabo et al. (1976) reported subacute effects of acrylonitrile in female Sprague-Dawley rats (200 g) exposed to the compound at 2000 ppm in the drinking water for 21 days. At this concentration of acrylonitrile, water intake was reduced in the experimental animals to one-third of that of the control animals. Limited pathological studies indicated atrophy of the zona fasciculata and increases in the zona glomerulosa of the adrenals. Elevated plasma Na^+ concentration of 9 mEq/l (K^+ was not changed) and reduced corticosterone concentrations of 24 μg (the denominator was not indicated) were noted. The authors concluded that acrylonitrile affected the mineral-corticoid and glucocorticoid cells of the adrenal cortex. Using the same strain of rats (Sprague-Dawley), Szabo et al. (1977) demonstrated a dose-dependent increase in glutathione levels following a 21-day exposure to water containing 20, 100 or 500 ppm acrylonitrile. It was suggested that this increase in glutathione was due to a rebound effect following the utilization of glutathione in the detoxification of acrylonitrile.

In a study by Quast et al. (1975), beagle dogs (four dogs of each sex at each exposure level) were exposed to 300, 200 and 100 ppm acrylonitrile in the drinking water for a 6-month period starting when the dogs were 8 months old. By using water consumption data, the mean doses of acrylonitrile ingested at the three exposure levels were for male dogs 18±4, 16±2, and 10±1 mg/kg/day, respectively, and for female dogs 18±5, 17±2, and 8±1 mg/kg/day, respectively. The two highest exposure levels (300 and 200 ppm) were highly toxic to the dogs; 3/4 males and 2/4 females at the 300 ppm level and 2/4 males and 3/4 females at the 200 ppm levels either died spontaneously or were euthanized because of their debilitated state Before 3 months (the ingested dose of acrylonitrile at these exposure levels was nearly identical). Two male dogs at the 300 ppm exposure level were removed from the study at 57 days because of signs of overt toxicity and were given water containing no acrylonitrile. These dogs appeared to recover completely (they regained their pretest weight) and, after removal from acrylonitrile exposure for ≈1 month, they were returned to the study. Subsequently, the dogs again showed signs of toxicity and died within 24 and 45 days. All dogs that died showed the following progression of signs: terminal depression, lethargy, weakness, emaciation and respiratory distress. Dogs that ingested water containing 100 ppm acrylonitrile and dogs that survived treatment at the higher doses appeared normal during the period of study.

The presence of acrylonitrile in the drinking water caused a significant decrease in water and food consumption in both male and female dogs at the

300 ppm level. At the other exposure levels, male dogs showed normal water and food consumption, while female dogs had sporadically lower water consumption and consistently lower food consumption. A supplemental study, which used eight female dogs that ingested water containing 100 ppm acrylonitrile, failed to demonstrate any decrease in either food or water consumption. With regard to general weight gains (only surviving animals were considered since emaciation was a symptom ensued by morbidity), all male dogs gained weight, although less than that gained by control animals, while female dogs lost weight, except for the animals at the 100 ppm exposure levels. It was not clear whether the unpalatability of water containing acrylonitrile may have affected these results.

Chemical studies on blood and urine samples revealed no significant abnormalities that were associated directly with acrylonitrile treatment; however some hematologic changes occurred at the higher exposure levels and were consistent with bronchopneumonia, which was chronically present (and the reason for death) in the high-dosed animals. Analysis of the liver and kidneys for nonprotein sulfhydryl content revealed no statistical differences in the animals at the 100 ppm exposure levels and no apparent effect at other doses, although these data could not be analyzed statistically because of the small group size. There was also no difference in the immunologic status of treated animals as assessed by percent of albumin, alpha 1, alpha 2, beta and gamma globulin in the serum.

On autopsy, some minor or indirectly-caused pathological findings were noted. In male dogs at the 100 and 200 ppm exposure levels, there was an increase in the relative kidney-to-body weight ratio (there were no changes in the only male dog exposed to 300 ppm acrylonitrile). The kidney appeared normal on histological examination and the weight gain may have been compensatory. There was also a decrease in the relative brain weight of the two surviving male dogs at the 200 ppm exposure level and an increase in the relative brain weight of the two surviving female dogs at the 300 ppm exposure level. No mention was made of results from histological examination of these brains. The lungs of dogs at the higher exposure levels showed typical pathologies of foreign body bronchopneumonia, the cause of which appeared to be aspirated food particles. The only treatment-related pathology was dilation, thinning of the walls and focal erosions or ulcerations of the esophagus in male and female dogs in the 300 and 200 ppm exposure groups. In some animals, although not consistently, there was a thickening of the epithelium lining of the dorsal surface of the tongue. It was believed that acrylonitrile may have caused irritation of the membrane of the throat, resulting in the aspiration of food particles.

The carcinogenicity studies discussed in Section 5.1 provide some data on nonneoplastic effects of chronic exposure to acrylonitrile. In the studies by Bio/dynamics, Inc. (1980a,b,c), groups of 100 male and 100 female Spartan or Fischer 344 rats were treated with acrylonitrile in the drinking water at concentrations of 1-300 ppm or by gavage at 0.1 and 10.0 mg/kg/day, 5 days/week for 19-26 months. The equivalent doses in the drinking water studies and the treatment-related gross and clinical observations of all three studies are given in Table 5-12.

The consistently observed increased mortality in animals ingesting acrylonitrile at 8-10 mg/kg/ day resulted from the debilitating effects of tumors in these groups of animals. The other effects observed, decreased body weight and changes in hematologic and urine values, were small in magnitude and in many cases could be attributed to the decrease in food and

TABLE 5-12

Toxicologic Findings in Rats in Three Oral Studies Performed*

Dose (mg/kg/day)	Sex	Mortality	Body Weight (% change)	Consumption		Hematology				Urinalysis	
				Food	Water	Hemoglobin	Hematocrit	Erythrocyte Count	Reticulocyte Count	Alkaline Phosphatase	Specific Gravity
7.98	M	I	D(10%)	D	D	D	D	D	ND	ND	ND
0.093	M	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
10.69	F	I	D(8%)	D	D	D	D	D	ND	ND	ND
0.146	F	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
8.37	M	I	D(12%)	D	D	ND	ND	ND	ND	I	I
2.49	M	ND	D(<5%)	ND	ND	ND	ND	ND	ND	ND	ND
0.84	M	I	ND	ND	ND	ND	ND	ND	ND	ND	ND
0.25	M	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
0.08	M	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
10.89	F	I	D(12%)	D	D	D	D	D	ND	I	ND
3.65	F	I	ND	ND	ND	ND	ND	ND	ND	I	ND
1.25	F	ND	ND	ND	ND	ND	ND	ND	ND	I	ND
0.36	F	I	ND	ND	ND	ND	ND	ND	ND	ND	ND
0.12	F	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
10.0	M	I	D(<6%)	D	ND	D	D	D	I	ND	ND
0.1	M	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
10.0	F	I	ND	ND	I	D	D	D	I	ND	ND
0.1	F	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

*Bio/dynamics, Inc. (1980a,b,c)

ND = No difference from control values; I = increase; D = decrease water consumption. Relative organ weights of the liver and kidney (organ-to-body weight ratio) were increased in the high-dose males and females; however, the absolute organ weights were either the same as control values or only slightly increased. Similar increases in relative and absolute organ weight were noted for the heart in the high-dose groups in two of the studies (Bio/dynamics, 1980b,c). The lack of pair-fed controls makes interpretation of these observations difficult.

In the previously discussed carcinogenicity study (see Section 5.1) conducted by Dow Chemical Company, Quast et al. (1980a) exposed 48 male and 48 female Sprague-Dawley rats to drinking water containing 0, 35, 85 or 210 ppm acrylonitrile for 2 years. After 21 days of exposure, the concentrations of acrylonitrile were changed to 0, 35, 100 or 300 ppm. The calculated amount of acrylonitrile ingested was 0, 3.42, 8.53 or 21.18 mg/kg/day for male rats and 0, 4.36, 10.76 or 24.97 mg/kg/day for female rats. By 9 months of treatment, animals treated with 100 and 300 ppm doses had rough hair coats and an unthrifty appearance. There was a treatment-related early mortality in female rats at all dose levels and in male rats at 300 ppm (see Table 5-1).

There was a significant dose-related decrease in daily water consumption of both male and female rats exposed to acrylonitrile. This decrease was probably due to voluntary restriction of intake as a result of an unpalatable taste imparted by acrylonitrile. The lower water consumption in treated rats was the probable cause of the concomitant decrease in food consumption and body weight. Chronic renal disease, which was common in older rats of this strain, occurred less frequently in treated rats probably as a result of the lower consumption of food and water. With this decrease in renal disease, there was a decrease in both gross and microscopic pathologies and clinical findings associated with renal failure. Decreased food and water consumption resulted in emaciation of the animals, which caused other clinical signs and pathologies to change.

The majority of clinical chemistry and pathological changes that occurred at a statistically significant level ($p=<0.05$) were attributed to secondary effects of treatment and were not considered to be caused by a toxic action of acrylonitrile. Although it was proposed that these changes were, for the most part, a result of restricted food and water consumption, it was impossible to state this unequivocally because of the lack of pair-fed controls. There were no severe or irreversible nontumorigenic pathological findings. The only nontumorigenic changes that were considered treatment-related included hyperplasia and hyperkeratosis of the squamous epithelium of the nonglandular portion of the stomach (100 and 300 ppm males and all treatment levels in females), proliferation of glial cells in the brain (300 ppm males and 35 and 100 ppm females) and mammary gland hyperplasia (300 ppm females).

Quast et al. (1980b) also conducted a 2-year inhalation carcinogenicity study in Sprague-Dawley rats, which was discussed previously in Section 5.1. Groups of 100 male and 100 female rats were exposed to acrylonitrile vapors at 0, 20 ppm (43 mg/m^3) and 80 ppm (174 mg/m^3), 6 hours/day, 5 days/ week. The rats were observed throughout the study for adverse effects of treatment as indicated by gross signs of unthrifty appearance and periodic examination of clinical chemistry and blood and urine parameters. The rats were killed at the end of 2 years or when moribund for gross and histologic examination.

During the course of exposure the animals both in the 20 ppm (43 mg/m^3) and 80 ppm (174 mg/m^3) groups showed a dose-related decrease in growth rate, early mortality, and a general unthrifty appearance. In the early portion of the study, there was an increase in water consumption in exposed animals. It was suggested that this increased water consumption resulted in an early onset of chronic renal disease, a commonly observed condition in older rats of this strain, in animals exposed to 20 ppm (43 mg/m^3) of acrylonitrile. Chronic renal disease was not seen at 80 ppm (174 mg/m^3) because of early mortality. It was considered that all clinical changes observed in the treated animals, whether increases or decreases, were related to the effects of chronic renal disease and not directly to acrylonitrile exposure. To fully understand the chronic toxicity of acrylonitrile, studies must be performed with pair-fed controls that are in the same nutritional state as the experimental animals, and evaluation of clinical signs must be made in the absence of gross neoplasias.

5.6. OTHER RELEVANT INFORMATION

Nonfatal intoxication by acrylonitrile has been reported in workers who clean polymerizers in plants that manufacture synthetic rubber (Wilson, 1944; Wilson et al., 1948). The workers were exposed to between 16 and 100 ppm of acrylonitrile for periods of 20-45 minutes. The most frequent symptoms were nasal irritation, respiratory difficulties, dull headache, nausea and nervous irritability. In a more severe case of intoxication, a low grade anemia and mild jaundice occurred. All exposed workers appeared to recover fully, with the exception of one who had severe jaundice. Similar symptoms of headache, vertigo, nausea and vomiting were reported by a chemist engaged in distilling acrylonitrile (Santorelli, 1966). Tremors, uncoordinated movement and convulsions were also experienced. As with other cases of intoxication, complete recovery occurred. Baxter (1979) summarized the symptoms of acrylonitrile poisoning in man as follows: irritation of eyes and nose, limb weakness, labored breathing, dizziness, impaired judgement, cyanosis, nausea, collapse, irregular breathing and convulsions, possibly followed by cardiac arrest. Recently, Doessing and Ranek (1984) reported that three workers developed jaundice 2-4 months after beginning work at a chemical plant. Liver biopsies showed severe centrilobular, hemorrhagic liver cell necrosis. The pathological changes were resolved within 6-18 months and no damage to other organs was observed. The workers were exposed to carbon disulphide, isopropanol, toluene and acrylonitrile; therefore, it was not possible to determine which chemical was responsible. Other case histories of occupational exposure to acrylonitrile are presented in IARC (1979).

Five cases of acute lethal intoxication have been reported (Davis et al., 1973) following fumigation of domiciles with acrylonitrile mixed with either 66% carbon tetrachloride or 70% methylene chloride (v/v). It was not clear, however, if acrylonitrile or the other component of the fumigant was the causitive agent in these deaths.

In a report of four case histories of human disease following fumigation of domiciles with acrylonitrile and carbon tetrachloride mixtures, Radimer et al. (1974) described the appearance of toxic epidermal necrolysis. Although a participating role for carbon tetrachloride could not be overruled, the lack of reports of epidermal disease following carbon tetrachloride exposure caused the authors to suspect that acrylonitrile was the toxic agent.

Acrylonitrile is a highly toxic compound to laboratory animals, regardless of the route of administration. Toxic levels of acrylonitrile reported for different species are summarized in Table 5-13. Acrylonitrile produces adrenal hemorrhagic necrosis within 90-120 minutes when given intravenously

TABLE 5-13

Toxic Levels of Acrylonitrile for Different Species

Species	Route	Effect	Dose	Reference
Rat	oral	LD_{50}	113 mg/kg	Smyth et al., 1969
	oral	LD_{50}	69.6 mg/kg	Stasenkova et al., 1978
	subcutaneous	LD_{50}	80 mg/kg	Knobloch et al., 1972
	intraperitoneal	LD_{50}	100 mg/kg	Knobloch et al., 1972
	inhalation	LD_{50}	0.47 mg/ℓ	Knobloch et al., 1972
Mouse	oral	LD_{50}	27 mg/kg	U.S. EPA, 1980
	intraperitoneal	LD_{Lo}	10 mg/kg	U.S. EPA, 1980
	intraperitoneal	LD_{50}	46 mg/kg	Willhite and Smith, 1981
	inhalation	LC_{Lo}	784 ppm, 1 hour	U.S. EPA, 1980
	inhalation	LD_{50}	0.30 mg/ℓ	Knobloch et al., 1972
Guinea pig	oral	LD_{50}	50 mg/kg	U.S. EPA, 1980
	inhalation	LC_{50}	576 ppm, 4 hours	U.S. EPA, 1980
	inhalation	LD_{50}	0.99 mg/ℓ	Knobloch et al., 1972
Dog	inhalation	LC_{Lo}	110 mg/kg, 4 hours	U.S. EPA, 1980
Cat	inhalation	LC_{Lo}	600 ppm, 4 hours	U.S. EPA, 1980
Rabbit	oral	LD_{50}	93 mg/kg	U.S. EPA, 1980
	inhalation	LC_{Lo}	258 ppm, 4 hours	U.S. EPA, 1980
	dermal	LD_{50}	250 mg/kg	U.S. EPA, 1980

to rats (Szabo et al., 1980, 1982), gastric, hepatic and duodenal lesions in rats (Szabo et al., 1983; Ghanayem and Ahmed, 1983; Ghanayem, 1983; Szabo and Gallagher, 1984; Silver et al., 1982b) and shows CNS excitatory properties (Szabo et al., 1982).

Acrylonitrile is a cyanoethylating agent that binds directly to tissue nucleophiles in the absence of metabolic activation (Hashimoto and Kanai, 1972). In vivo, acrylonitrile causes a reduction in glulathione (Szabo et al., 1977) and when given simultaneously with styrene increases serum creatinine and serum glutamic-oxaloacetic transaminase in a supraadditive manner (Normandeau et al., 1984).

Several authors (Ahmed and Patel, 1981; Willhite and Smith, 1981; Tanii and Hashimoto, 1984) suggested that the mixed function oxidase system metabolizes acrylonitrile to cyanide ion. Jaeger and Cote (1982) suggested that hypoxia inhibits mixed function oxidase activity and demonstrated increased mortality in rats exposed to hypoxia and acrylonitrile.

Szabo and Selye (1972) demonstrated in female rats that the adrenal apoplexy and mortality induced by acrylonitrile are prevented by phenobarbital pretreatment. Adrenal lesions are eliminated by some glucocorticoids (dexamethasone and betamethasone) but these are effective in preventing death. Cote et al. (1983) reported that pretreatment by inhalation with sublethal concentrations of acrylonitrile protects rats from subsequent lethal acrylonitrile exposures.

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

Data regarding the acute toxicity of acrylonitrile to aquatic organisms has been established for eight species of freshwater fish, one species of saltwater fish and six species of freshwater crustaceans.

Henderson et al. (1961), investigating the response of fathead minnows, *Pimephales promelas*, exposed to nominal concentrations of acrylonitrile, reported the results of three 96-hour toxicity tests. The 96-hour flow-through LC_{50} value was determined to be 10.1 mg/ℓ. The 96-hour static LC_{50} values of 14.3 and 18.1 mg/ℓ were also reported. Marconi and Ionescu (1974) established 24- and 48-hour LC_{50} values of 37.4 and 24.0 mg/ℓ, respectively, for the common carp, *Cyprinus carpio*. The LC_{50} values of 28 and 13 mg/ℓ were established for the golden orfe, *Leuciscus idus melanotus*, at two independent laboratories (Juhnke and Leudemann, 1978). The 48-hour flowthrough LC_{50} value of 15 mg/ℓ was reported by Sloof (1979) for another cyprinid, the zebra danio, *Brachydanio rerio*. Wellens (1982) also established an LC_{50} value of 25 mg/ℓ for zebra danio; however, no additional information on duration or method of exposure was provided.

Tonogai et al. (1982) reported 24- and 48-hour LC_{50} values of 50 and 32 mg/ℓ, respectively, for a static method exposure of medaka, *Oryzias latipes*, to acrylonitrile at 25°C. The 96-hour static LC_{50} value of 33.5 mg/ℓ was determined by Henderson et al. (1961) for the guppy, *Poecilia reticulata*.

The results of investigations by Buccafusco et al. (1981), U.S. EPA (1978) and Henderson et al. (1961) into the response of bluegills, *Lepomis* macrochirus, to 96-hour static exposures to acrylonitrile are in close agreement (Table 6-1). The 96-hour LC_{50} values of 10.1 and 11.8 mg/ℓ were reported by the U.S. EPA (1978) and Henderson et al. (1961), respectively. Buccafusco et al. (1981) reported the 96- and 24-hour LC_{50} values of 10 and 28 mg/ℓ, respectively, for fish maintained at 22°C. Buzzel et al. (1968) reported no mortality of bluegills exposed to acrylonitrile at concentrations up to 10 mg/ℓ, near the apparent threshold level.

Sloof (1979) established an EC_{50} value of 5 mg/ℓ acrylonitrile based on the concentration necessary to inhibit respiration in rainbow trout, Salmo gairdneri, in a flowthrough system maintained at 20°C.

Daugherty and Garret (1951) determined the 24-hour LC_{50} value of 24.5 mg/ℓ for the salt-water species, the pinfish (Lagodon rhomboides).

LeBlanc (1980) and the U.S. EPA (1978) investigated the effects of acrylonitrile on the water flea, Daphnia magna (Table 6-2). LeBlanc (1980) used a standardized static toxicity exposure method maintained at 22°C and reported 24- and 48-hour LC_{50} values of 13 and 7.6 mg/ℓ, respectively. In a similar static toxicity test performed by the U.S. EPA (1978), the LC_{50} was determined to be 7.55 mg/ℓ.

Erben and Beader (1983) reported complete mortality of the snails, Lymnaea stagnalis and Radix peragra, within 24 hours of exposure to acrylonitrile at concentrations of 0.24 and 0.16 mg/ℓ, respectively.

D'Angelo and Signorile (1978) reported the results of investigations into the responses of three species of crustaceans exposed to acrylonitrile (Table 6-2). The crustaceans, Moina macracopo, Cypria ophthalmica and Cyclops sp., exhibited 95, 57, and 19% mortality when exposed to 2.0 mg/ℓ acrylonitrile for 96 hours at 20°C.

TABLE 6-1

Acute Lethal Effects of Acrylonitrile to Fish

Species	Duration (hours)	Concentration (mg/ℓ)	Method	Effect	Reference
Fathead minnow *Pimephales promelas*	96	14.3	static	LC_{50}	Henderson et al., 1961
	96	18.1	static	LC_{50}	Henderson et al., 1961
	96	10.1	flowthrough	LC_{50}	Henderson et al., 1961
Common carp *Cyprinus carpio*	24	37.4	NR	LC_{50}	Marconi and Ionescu, 1974
	48	24.0	NR	LC_{50}	Marconi and Ionescu, 1974
Golden orfe *Leuciscus idus melanotus*	NR	28	NR	LC_{50}	Juhnke and Leudemann, 1978
	NR	13	NR	LC_{50}	Juhnke and Leudemann, 1978
Zebra danio *Brachydanio rerio*	48	15	flowthrough	LC_{50}	Sloof, 1979
	NR	25	NR	LC_{50}	Wellens, 1982
Medaka *Oryzias latipes*	24	50	25°C; static	LC_{50}	Tonogai et al., 1982
	48	32	25°C; static	LC_{50}	Tonogai et al., 1982

TABLE 6-1 (cont.)

Species	Duration (hours)	Concentration (mg/ℓ)	Method	Effect	Reference
Guppy *Poecilia reticulata*	96	33.5	static	LC_{50}	Henderson et al., 1961
Bluegill *Lepomis macrochirus*	24	28	22±1°C; static	LC_{50}	Buccafusco et al., 1981
	96	10	22±1°C; static	LC_{50}	Buccafusco et al., 1981
	96	10.1	static	LC_{50}	U.S. EPA, 1978
Bluegill *Lepomis macrohirus*	96	11.8	static	LC_{50}	Henderson et al., 1961
	96	10	NR	no mortality	Buzzell et al., 1968
Rainbow trout *Salmo gairdneri*	24	5	20±1°C; flowthrough	EC_{50}	Sloof, 1979
Pinfish *Lagodon rhomboides*	24	24.5	NR	LC_{50}	Daugherty and Garrett, 1951

NR = Not reported

TABLE 6-2

Toxic Effects of Acrylonitrile to Aquatic Invertebrates

Species	Duration (hours)	Concentration (mg/ℓ)	Method	Effect	Reference
Water flea *Daphnia magna*	24	13	22±1°C; static	LC_{50}	LeBlanc, 1980
	48	7.6	22±1°C; static	LC_{50}	LeBlanc, 1980
	48	7.55	static	LC_{50}	U.S. EPA, 1978
Snail *Lymnaea stagnalis*	24	0.24	NR	LC_{100}	Erben and Beader, 1983
Snail *Radix peragra*	24	0.16	NR	LC_{100}	Erben and Beader, 1983
Crustaceaus *Moina macracopo*	96	2.0	20°C	95% mortality	D'Angelo and Signorile, 1978
Cypria ophthalmica	96	2.0	20°C	57% mortality	D'Angelo and Signorile, 1978
Cyclops sp.	96	2.0	20°C	19% mortality	D'Angelo and Signorile, 1978

NR = Not Reported

6.2. CHRONIC EFFECTS

Fathead minnows exposed to acrylonitrile for 30 days in a flowthrough tox- icity system had an LC_{50} value of 2.6 mg/ℓ (Henderson et al. 1961) Table 6-3). The U.S. EPA (1978) established that the MATC for the water flea was >3.6 mg/ℓ.

6.3. PLANT EFFECTS

Data regarding the effects of acrylonitrile on aquatic plants or algae were not located in the available literature as cited in the Appendix.

6.4. RESIDUES

The bioconcentration potential of acrylonitrile in bluegills was investigated by Veith et al. (1980a, Table 6-3). The BCF of 48 was determined by analysis of whole body tissues upon stabilization of the steady-state level after 28 days of exposure (Table 6-3).

6.5. OTHER RELEVANT INFORMATION

Additional data on the effects of acrylonitrile to aquatic organisms were not located in the available literature as cited in the Appendix.

TABLE 6-3

Chronic Effects and Residual Acrylonitrile in Aquatic Organisms

Species	Duration (days)	Concentration (mg/ℓ)	Method	Effect	Reference
Fathead minnow Pimephales promelas	30	2.6	flowthrough	LC_{50}	Henderson et al., 1961
Water flea Daphnia magna	NR	>3.6	flowthrough	MATC	U.S. EPA, 1978
Bluegill Lepomis macrochirus	28	48	whole tissue	BCF	Veith et al., 1980a

NR = Not Reported

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMANS

The ACGIH (1984) has adopted a TWA-TLV for occupational exposure to acrylonitrile of 2 ppm (~4.5 mg/m³) with the notation that cutaneous absorption contributes to exposure. Furthermore, the ACGIH (1984) cautions that acrylonitrile is a suspected carcinogen (A2). The TLV was recommended based on the observations that acrylonitrile consistently produces tumors in rats and that epidemiology studies raise the suspicion that acrylonitrile is carcinogenic to humans. According to the ACGIH (1980), the current OSHA standard is 2 ppm (~4.5 mg/m³) for an 8-hour TWA and the ceiling limit is 10 ppm (~22 mg/m³) for 15 minutes.

7.2. AQUATIC

Available data for acrylonitrile indicate that acute and chronic toxicity to freshwater aquatic life occur at concentrations as low as 7.55 and 2.6 mg/ℓ, respectively, and would occur at lower concentrations among species that are more sensitive than those tested.

Only one saltwater species has been tested with acrylonitrile and no statement can be made concerning acute or chronic toxicity.

8. RISK ASSESSMENT

The oral and inhalation rat bioassays of acrylonitrile (Quast et al., 1980a,b; Bio/dynamics Inc., 1980a,b,c) have all shown significant increases in brain and spinal cord astrocytomas, Zymbal gland carcinomas and stomach papillomas/carcinomas. Occupational exposure to acrylonitrile has been associated with the induction of respiratory cancers (O'Berg, 1980). These studies are discussed in Section 5.1. and the tumor incidences are presented in Tables 5-2, 5-3, 5-4, 5-5, 5-8 and 5-9.

The mutagenicity of acrylonitrile has been demonstrated in the *Salmonella typhimurium*/microsome assay system (Milvy and Wolff, 1977; De Meester et al., 1978, 1979; Cerna et al., 1981). In the absence of metabolic activation, acrylonitrile has no mutagenic effect toward any of the tested *Salmonella* strains. Direct mutagenicity of the compound was noted in some strains of *Escherichia coli* (Venitt et al., 1977). *In vivo* experiments have shown that urine from acrylonitrile pretreated rats exerted a direct mutagenic activity towards *Salmonella* (Lambotte-Vandepaer et al., 1980, 1981). In *in vitro* experiments, acrylonitrile induced DNA strand breakage and cell transformation in Syrian golden hamster embryo cells (Parent and Casto, 1979) and increased sister chromatid exchanges in human lymphocytes (Perocco et al., 1982) when the cells were co-cultivated with an activating system. A dominant lethal test to detect chromosomal aberrations in male mice germ cells yielded negative results (Leonard et al., 1981; Rabello-Gay and Ahmed, 1980). Thiess and Fleig (1978) failed to exhibit evidence of increased chromosomal aberrations in peripheral lymphocytes of 18 workers who had been occupationally exposed to acrylonitrile for 15.3 years.

Results of an extensive 3-generation reproductive study on rats (Beliles et al., 1980) showed no compound related effects with the exception of reduced food and water consumption and body weight gain of the parental generation and death of F_1 pups at a drinking water level of 500 ppm. No increased mortality occurred in other generations. Fetal malformations were observed in the offspring of rats that received 65 mg/kg but not $\leq$25 mg/kg acrylonitrile by gavage during gestation (Murray et al., 1978).

Dogs treated with acrylonitrile in the drinking water for 6 months had increased mortality and reduced food and water intake at 300 ppm, increased relative kidney weight at $\geq$100 ppm, decreased relative brain weight and esophageal lesions at $\geq$200 ppm (Quast et al., 1975). Rats treated with acrylonitrile in the drinking water for 2 years had early mortality at $\geq$35 ppm and rough hair and unthriftiness at $\geq$100 ppm. Nonneoplastic lesions included hyperplasia and hyperkeratosis of the stomach squamous epithelium and proliferation of brain glial cells at $\geq$35 ppm and mammary gland hyperplasia at 300 ppm.

Inhalation exposure of rats to 43 and 174 mg/m^3, 6 hours/day, 5 days/week for 2 years was associated with decreased growth rate, early mortality and general unthriftiness (Quast et al., 1980b). Subchronic inhalation exposure of rats, guinea pigs, rabbits, cats and monkeys to acrylonitrile at $\geq$217 mg/m^3, 4 hours/day, 5 days/week for 8 weeks resulted in renal, liver and lung effects (Dudley et al., 1942). At 332 mg/m^3, severe signs of toxicity and death occurred. Hematologic changes were observed in rats and rabbits at subchronic inhalation exposures of ~50 mg/m^3 (Minami et al., 1973; Knoblock et al., 1972).

The U.S. EPA (1983a) calculated three cancer potency factors for acrylonitrile: a B_H based on the epidemiologic study of O'Berg (1980), a q_1^* based on the geometric mean of the q_1^* values obtained from the rat drinking water studies of Quast et al. (1980a) and Bio/dynamics, Inc., (1980a,b) and a q_1^* based on the with rat inhalation study of Quast et al. (1980b). The value for B_H was determined to be 1.5×10^{-4} $(ppb)^{-1}$ or 6.8×10^{-3} $(\mu g/m^3)^{-1}$. Therefore, the lifetime risk of cancer for people exposed continuously to 1 ppb is 1.5×10^{-4} or to 1 $\mu g/m^3$ is 6.8×10^{-3}.

The U.S. EPA (1983a) calculated values for the q_1^* for each of the drinking water studies using the combined incidences of brain and spinal cord astrocytomas, Zymbal gland carcinomas and stomach tumors for each of the studies by Bio/dynamics Inc., (1980a,b) and for the total number of tumors, excluding mammary gland, in the Quast et al. (1980a) study. Separate values were obtained for males and females and the geometric means of the three q_1^* values for males and the three q_1^* values for females were taken (Table 8-1). Because the geometric mean for the male values was the larger, the q_1^* of 5.4×10^{-1} $(mg/kg/day)^{-1}$ was recommended for estimating an increased lifetime risk of human exposure by the oral route to acrylonitrile, (U.S. EPA, 1983a). Because no additional data regarding the carcinogenicity of acrylonitrile has become available, no change in the q_1^* is suggested.

TABLE 8-1

Estimate of q_1^* For Three Drinking Water Studies in Rats*

q_1^* in $(mg/kg/day)^{-1}$ Males	Females	Reference
9.9×10^{-1}	9.2×10^{-1}	Quast et al., 1980a
4.0×10^{-1}	3.7×10^{-1}	Bio/dynamics Inc., 1980a
4.0×10^{-1}	2.9×10^{-1}	Bio/dynamics Inc., 1980b
5.4×10^{-1}	4.6×10^{-1}	Geometric Average

*Source: U.S. EPA, 1983a

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

Several chronic toxicity studies were available for consideration in deriving CSs and RQs for acrylonitrile. These studies were discussed in Section 5.5. and summarized in Table 9-1. The doses in mg/kg/day from inhalation studies (Table 9-1) were calculated by expanding the exposures over a 24-hour day and a 7-day week by multiplying by the animal inhalation rate and dividing by the animal body weight. The animal inhalation rates used in the calculation were 0.40 m^3/day for guinea pigs, 2.0 m^3/day for rabbits, 1.2 m^3/day for cats, 4.3 m^3/day for dogs and 5.4 m^3/day for monkeys (Durkin, 1985). The animal body weights were 0.84 kg for guinea pigs, 3.8 kg for rabbits, 3.0 kg for cats, 12.7 kg for dogs and 8.0 kg for monkeys (Durkin, 1985). To calculate the inhalation rate (I) for rats, the following equation, from Federal Register (1980) was used:

$$I(m^3/day) = [0.105(\text{rat weight}/0.113)^{2/3}]$$

For the studies of Dudley et al. (1942), Knobloch et al. (1972) and Babanov et al. (1972), the rat weight was assumed to be 0.35 kg (Federal Register, 1980; Durkin, 1985). For the study of Quast et al. (1980b), the average weights were estimated from the growth curves provided by Quast et al. (1980b) to be 0.56 kg for male rats and 0.38 kg for female rats.

The study of Quast et al. (1975), in which beagle dogs ingested drinking water containing 0, 100, 200 or 300 ppm acrylonitrile for up to 6 months, does not lend itself to the derivation of an RQ. A small number of experimental animals was used (four of each sex) and the levels of acrylonitrile used were either too toxic (five of eight animals in the two higher dose groups died before 3 months of exposure) or produced no adverse effects (low dose group).

TABLE 9-1

Toxicity Summary for Acrylonitrile

Route	Species/ Strain	Sex	No. at Start	Vehicle/ Physical State	Dosage/ Exposure	Dose (mg/kg/day)	Response	Reference
Oral	dogs/ beagles	M,F	12 M 12 F	drinking water	300, 200, 100 ppm for 6 months	males: 17±4, 16±2, 10±1 females: 18±5, 17±2, 8±1[a]	mortality at 300 ppm - 3/4 males; 2/4 females. mortality at 200 ppm - 3/4 females. 300 ppm - decreased H_2O and food consumption. 100 ppm group and all survivors of higher doses showed no overt signs of toxicity. All male dogs gained weight; all female dogs lost weight, but not at 100 ppm. In males at 100 and 200 ppm: increase in kidney-to-body weight ratio. In males at 200 ppm: decrease in relative brain weight. At 200 and 300 ppm dilation, thinning of the walls, focal erosions or ulcerations of the esophagus.	Quast et al., 1975
Oral	rat/Sprague-Dawley	M,F	48 M 48 F	drinking water	0, 35, 85 or 210 ppm for 21 days 0, 35, 100 or 300 ppm for 2 years	males: 0, 3.42, 8.53, or 21.18 female: 0, 4.36, 10.76 or 24.97[a]	early mortality in females at all doses and males at 300 ppm. At 100 and 300 ppm - rough hair coats and unthrifty appearance. Hyperplasia and hyperkeratosis of the squamous epithelium of nonglandular stomach (100 and 300 ppm males and all treatment females). Proliferation of glial cells in the brain (300 ppm males and 35 and 200 ppm females) and mammary gland hyperplasia (300 ppm females)	Quast et al., 1980a

TABLE 9-1 (cont.)

Route	Species/ Strain	Sex	No. at Start	Vehicle/ Physical State	Dosage/ Exposure	Dose mg/kg/day	Response	Reference
Oral	rat/ Spartan	M,F	100 M 100 F	drinking water	0, 1 or 100 ppm for ~2 years	0, 0.093 or 7.98 for males; 0, 0.146 or 10.69 for females[a]	organ weight changes, increased mortality, decreased body weight gain, food and water consumption, decreased hemoglobin, hematocrit and erythocyte count at high doses; effects probably secondary to neoplasia and poor nutritional state	Bio/dynamics, Inc. 1980a
Oral	rat/ Fischer 344	M,F	100 M 100 F	drinking water	0, 1, 3, 10, 30, or 100 ppm ~2 years	0, 0.08, 0.25, 0.84, 2.49 or 8.37 for males; 0, 0.12, 0.36, 1.25, 3.65 or 10.89 for females[a]	increased mortality at ≥0.36 mg/kg/day, decreased body weight gain and food and water intake, organ weight changes, changes in hematologic parameters and urinalysis at high dose secondary to neoplasia and poor nutritional state	Bio/dynamics, Inc. 1980b
Oral	rat/ Spartan	M,F	100 M 100 F	in water by gavage	0, 0.1 or 10 mg/kg/day, 5 days/week, for 20 months	0, 0.07 or 7.1	similar effects as in drinking water study	Bio/dynamics, Inc. 1980c
Oral	rat/ Sprague-Dawley	M,F	NR	gavage	0, 10, 25, 65 mg/kg/day on days 6-15 of gestation	0, 10, 25, 65	25 mg/kg/day - dams: slight thickening of nonglandular portion of the stomach; fetuses: right sided aortic arch in one fetus. 65 mg/kg/day - dams: decreased body weight, thickening of the nonglandular portion of the stomach, increased liver weight. fetuses: significant decrease in fetal body weight, significant decrease in crown-rump length, significant increase in combined incidence of acaudate and short-tailed fetuses, short trunk, anteriorly displaced ovaries, missing ribs and imperforate anus in experimental and control acaudate and short-tailed groups, right-sided aortic arch in one fetus.	Murray et al., 1978

TABLE 9-1 (cont.)

Route	Species/Strain	Sex	No. at Start	Vehicle/Physical State	Exposure	Dosage/Dose mg/kg/day	Response	Reference
Inhalation	rat/ Sprague-Dawley	F	NR	gas	80 ppm (174 mg/m^3) on days 6-15 of gestation	23^{b}	dams: no treatment-related toxic effects: fetuses: at 80 ppm - significant increase in all fetal malformations when considered collectively	Murray et al., 1978
Oral	rat/ Charles River	M,F	3 generations	drinking water	100 or 500 ppm	14 or 70^{c}	First generation - at 500 ppm - parents had decreased body weight gain, increased mortality of nursing pups in the first 2 matings. all other generations - pup survival and reproductive capacity normal; at 500 ppm all surviving pups had a decrease in body weight gain.	Bellies et al., 1980
Inhalation	rhesus monkey dogs/NR		NR NR	4 2	gas gas	56 ppm (122 mg/m^3) 4 hours/day, 5 days/week for 4 weeks	9.8 (monkey) 4.9 (dog)^{d}	monkey: no overt toxicity dog: 1 died during 1st exposure; 2nd had paralysis of hind leg after the 5th, 13th and 14th exposure period	Dudley et al. 1942
Inhalation	rats/NR guinea pigs/NR rabbits/NR cats/NR		NR NR NR NR	16 16 3 4	gas gas gas gas	100 ppm (217 mg/m^3) 4 hours/day, 5 days/week for 8 weeks	16 (rat) 12 (guinea pig) 14 (rabbit) 10 (cat)^{d}	rats and guinea pigs had slight lethargy; rabbits had no weight gain; cats vomited and lost weight; spleen of rats showed hemosiderosis; kidneys of all species showed renal irritation and subacute bronchopneumonia present in most species	Dudley et al., 1942
Inhalation	rats/NR guinea pigs/NR rabbits/NR cats/NR rhesus monkey/NR		NR NR NR NR NR	16 16 4 4 2	gas gas gas gas gas	153 ppm (332 mg/m^3) 4 hours/day, 5 days/week for 8 weeks	25 (rat) 19 (guinea pig) 21 (rabbit) 16 (cat) 27 (monkey)^{d}	severe toxicity noted in all animals; early mortality before completion of study spleen of rats showed hemosiderosis; kidneys of all species showed renal irritation and subacute bronchopneumonia present in most species	Dudley et al. 1942

TABLE 9-; (cont.)

Route	Species/ Strain	Sex	Start	Vehicle/ No. at State		Physical Exposure	Dosage/ mg/kg/day	Dose	Response	Reference
Inhalation	rats/NR rabbits/NR		NR NR	NR	gas	50 mg/m³ for 6 months	32 (rat) 26 (rabbit)[d]		In both rats and rabbits: changes in peripheral blood pattern, functional disorders in respiratory, cardiovascular and renal system as well as signs of neuron lesion in the CNS	Knobloch et al., 1972
Inhalation	rat/Sprague-Dawley		M,F	100 M 100 F	gas	20 or 80 ppm (43 or 174 mg/m³) 6 hours/day, 5 days/week for 2 years	4.2 or 16.9 for males[d], 4.8 or 19.3 for females[d]		dose-related decrease in growth rate, early mortality, unthriftiness, early onset of renal disease attributed to increased water consumption, clinical changes secondary to neoplasia	Quast et al., 1980b
Inhalation	rat/NR		NR	NR	gas	0.495 mg/m³, 5 hours/day, 6 days/week for 6 months	.056[d]		CNS disorders, hematologic and biochemical changes	Babanov et al., 1972

[a] The dose was calculated by the investigators from water intake and weight gain data.

[b] The dose was calculated by the investigators from measured blood levels of acrylonitrile.

[c] The dose was calculated by assuming that a rat drinks 0.049 ℓ/day (Durkin, 1985) and weighs 0.35 kg.

[d] The dose was calculated by assuming 100% absorption, expanding the disposure over a 24-hour day and 7-day week day multiplying by the animal inhalation rate and dividing by the animal body weight (see text).

NR = Not reported

An RQ cannot be derived for the chronic oral toxicity/carcinogenicity study of Quast et al. (1980a), in which rats ingested 0, 35, 100 or 300 ppm acrylonitrile in their drinking water for 2 years. Effects such as treatment-related early mortality could not be treated solely as a toxic effect as opposed to a carcinogenic effect; other effects appeared to be secondary to decreased water and food consumption. Further, there was no distinction made between toxic and carcinogenic effects. Therefore, it is impossible to assign a reliable RV_e to toxic effects observed in this study, which precludes the derivation of a CS or an RQ.

For similar reasons, an RQ cannot be derived from the chronic oral/carcinogenicity studies of Bio/dynamics, Inc., (1980a,b,c) or from the inhalation/carcinogenicity study of Quast et al. (1980b)

The inhalation studies of Dudley et al. (1942) are not suitable for RQ derivation because the effects of early mortality and signs of CNS toxicity represented acute responses to relatively high exposures.

The inhalation studies of Knobloch et al. (1972) and Babanov et al. (1972) also are not suitable for the derivation of an RQ. These studies were summarized in U.S. EPA (1980) and lack sufficient details regarding experimental design and toxic effects.

RQs were derived for the oral and inhalation teratogenicity studies of Murray et al. (1976, 1978) and for the oral 3-generation study of Beliles et al. (1980). These values and the corresponding CSs are summarized in Table 9-2. The animal doses in units of mg/kg/day were multiplied by the cube root of the ratio of the animal body weight to the human weight (assuming mean body weights of 0.35 kg for rats and 70 kg for humans) and 70 kg to estimate a human MED. An uncertainty factor of 10 was applied to the animal exposures to calculate a corresponding chronic human MED from short-term

TABLE 9-2

Composite Scores for the Oral and Inhalation Toxicity of Acrylonitrile

Species	Route	Animal Dose	Human MED (mg/day)*	RV_d	Effects	RV_e	CS	RQ	Reference
Rat	oral	25 mg/kg/day days 6-15 of gestation	29.9	3.3	dams: slight thickening of the nonglandular portion of the stomach; fetuses: right-sided aortic arch in one fetus.	9	30	100	Murray et al., 1976
Rat	oral	70 mg/kg/day 3-generations	83.8	2.6	decreased body weight gain of parents of first generation; increased mortality of first generation nursing pups	10	26	100	Belliles et al., 1980
Rat	inhalation	23 mg/kg/day days 6-15 of gestation	27.5	3.3	dams: no treatment-related toxic effects; fetuses: significant increase in all fetal malformations when considered collectively	10	33	100	Murray et al., 1978

*An uncertainty factor of 10 was applied to calculate corresponding chronic human MEDs from short-term exposures used in teratogenicity studies.

exposures used in the teratogenicity and reproduction studies because the toxicity to adult animals of such high levels of acrylonitrile exposure over long periods of time is inadequately characterized. Chronic studies have demonstrated carcinogenic response but little evidence of nonneoplastic toxic effects at exposure levels <25 mg/kg/day (oral) and at 174 mg/m³ (inhalation). A corresponding RV_d was calculated for the human MED. Depending upon the observed toxic effects, an RV_e was assigned. The CS was then calculated as the product of the RV_d and RV_e.

All of the CSs (26-33) correspond to an RQ of 100; however, the highest CS of 33 was obtained from the inhalation teratogenicity study (Table 9-3). In a previous determination of the RQ (U.S. EPA, 1983b), both the oral and the inhalation teratogenicity studies yielded CSs of 30, and the oral data were used to recommend the RQ. In the previous determination, (U.S. EPA, 1983b) the inhalation exposures yielded slightly different MEDs Because of small differences in the estimates of inhaled animal doses. This difference in dose estimation accounts for the current CS of 33 vs. the previous CS of 30.

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

Studies on the carcinogenicity of acrylonitrile are summarized in Tables 9-4 to 9-9.

In addition, an epidemiological study was conducted at a DuPont textile fibers plant (O'Berg, 1980). The study cohort consisted of 1345 male employees who had potential exposure to acrylonitrile at some time between start-up of the plant in 1950 and 1966. The cut-off date allowed for a minimum 10-year follow-up through the end of 1976. As discussed by U.S. EPA (1983a), the levels of exposure were designated as high (20 ppm or 43 mg/m³), medium (10 ppm or 22 mg/m³) and low (5 ppm or 11 mg/m³). Overall, 25 cases of cancer occurred, with 20.5 expected based on company rates

TABLE 9-3

Acrylonitrile

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	inhalation
Dose[a]:	27.5 mg/day
Effect:	teratogenicity without maternal toxicity
Reference:	Murray et al., 1978
RV_d:	3.3
RV_e:	10
Composite Score:	33
RQ:	100

[a] Equivalent Human Dose

TABLE 9-4

Incidence of Tumors in Sprague-Dawley Rats given Acrylonitrile Orally for 24 months[a]

Sex	Dose or Exposure (mg/kg/day)	Duration of Treatment (months)	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)[d]
M	0.0	NA	NA	NA	brain/spinal cord	astrocytoma	1/80
					Zymbal gland	carcinoma	3/80
					stomach	all tumors	0/80
					tongue	squamous cell tumors	1/75
M	3.42[c]	24	high purity[d]	drinking water	brain/spinal cord	astrocytoma	12/47 (p<0.05)
					Zymbal gland	carcinoma	4/47
					stomach	all tumors	3/46 (p<0.05)
					tongue	squamous cell tumors	2/7[e]
M	8.53[c]	24	high purity[d]	drinking water	brain/spinal cord	astrocytoma	22/48 (p<0.05)
					Zymbal gland	carcinoma	3/48
					stomach	all tumors	23/48 (p<0.05)
					tongue	squamous cell tumors	4/9[e] (p<0.05)
M	21.18[c]	24	high purity[d]	drinking water	brain/spinal cord	astrocytoma	30/48 (p<0.05)
					Zymbal gland	carcinoma	15/48
					stomach	all tumors	39/47 (p<0.05)
					tongue	squamous cell tumors	5/40[e] (p<0.05)
F	0.0	NA	NA	NA	brain/spinal cord	astrocytoma	0/80
					Zymbal gland	carcinoma	1/80
					stomach	all tumors	1/80
					tongue	squamous cell tumors	0/78
					mammary gland	malignant/benign	57/80
F	4.36[e]	24	high purity[d]	drinking water	brain/spinal cord	astrocytoma	17/48 (p<0.05)
					Zymbal gland	carcinoma	4/48
					stomach	all tumors	1/47
					tongue	squamous cell tumors	1/48
					mammary gland	malignant/benign	42/48 (p<0.05)

TABLE 9-4 (cont.)

Sex	Dose or Exposure (mg/kg/day)	Duration of Treatment (months)	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Tumor Type	Incidence (p value)[b]
F	10.76[c]	24	high purity[d]	drinking water	brain/spinal cord	astrocytoma	22/48 ($p<0.05$)
					Zymbal gland	carcinoma	6/48
					stomach	all tumors	12/48 ($p<0.05$)
					tongue	squamous cell tumors	1/5[e]
					mammary gland	malignant/benign	42/48 ($p<0.05$)
F	24.97[c]	24	high purity[d]	drinking water	brain/spinal cord	astrocytoma	24/48 ($p<0.05$)
					Zymbal gland	carcinoma	14/48 ($p<0.05$)
					stomach	all tumors	30/48 ($p<0.05$)
					tongue	all tumors	2/3[e] ($p<0.05$)
					mammary gland	malignant	35/48

QUALITY OF EVIDENCE

Strengths of Study:	The compound was administered for lifetime by a natural route to both sexes at three dose levels. Complete histologic examinations were performed. Tumors incidence appeared dose related in both sexes. Statisical analyses were performed.
Weakness of Study:	Animals in the two high dose groups had poor food and water consumption.
Overall Adequacy:	Adequate

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[a] Quast et al., 1980a; U.S. EPA, 1983a

[b] Tumor incidence expressed as number of rats bearing tumors/the number of rats examined microscopically for that particular organ.

[c] The dose was calculated from measured water consumption and body weight.

[d] The acrylonitrile was stablized with hydroquinone monoethyl ether (39 ppm).

[e] All samples were not taken from all animals

NA = Not applicable

TABLE 9-5

Incidence of Tumors in Spartan Rats given Acrylonitrile Orally[a]

Sex	Dose or Exposure (mg/kg/day)	Duration of Treatment (months)	Duration of Study (months)	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)
M	0.0	NA	22	NA	NA	brain Zymbal gland stomach	astrocytoma carcinoma papilloma/carcinoma	2/98 1/100 3/98
M	0.093[b]	22	22	100%[c]	drinking water	brain Zymbal gland stomach	astrocytoma carcinomas papilloma/carcinoma	3/95 0/91 3/98
M	7.98[b]	22	22	100%[c]	drinking water	brain Zymbal gland stomach	astrocytoma carcinomas papilloma/carcinoma	23/97 ($p<0.05$) 14/93 ($p<0.05$) 12/97 ($p<0.05$)
F	0.0	NA	22	NA	NA	spinal cord brain Zymbal gland stomach	astrocytoma astrocytoma carcinomas papilloma/carcinoma	0/96 0/99 0/99 1/100
F	0.146[b]	19	19	100%[c]	drinking water	spinal cord brain Zymbal gland stomach	astrocytoma astrocytoma carcinomas papilloma/carcinoma	0/99 1/100 0/95 4/99
F	10.69[b]	19	19	100%[c]	drinking water	spinal cord brain Zymbal gland stomach	astrocytoma astrocytoma carcinomas papilloma/carcinoma	7/98 ($p<0.05$) 32/97 ($p<0.05$) 7/98 ($p<0.05$) 7/99 ($p<0.05$)

QUALITY OF EVIDENCE

Strengths of Study: The compound was administered by a natural route for the lifespan of the animals to both sexes at 2 dose levels. The level of acrylonitrile in the drinking water was routinely monitored by GC. Extensive histopathology was performed.

Weakness of Study: Early mortality required shortening the study from 24 months to 19-20 months.

Overall Adequacy: Adequate

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[a] Bio/dymanics Inc., 1980a; U.S. EPA, 1983a

[b] The dose was calculated from measured water consumption and body weight.

[c] The authors reported that the acrylonitrile was "100% active ingredient".

NA = Not applicable

TABLE 9-6

Incidence of Tumors in Fisher Rats given Acrylonitrile Orally

Sex	Dose or Exposure (mg/kg/day)	Duration of Treatment (months)	Duration of Study (months)	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)
M	0.0	NA	26	NA	NA	brain	astrocytoma	2/200
						ear canal	carcinoma/adenoma	2/89
						stomach	all tumors	0/199
						spinal cord	astrocytoma	1/196
M	0.08^b	26	26	100%^{c}	drinking water	brain	astrocytoma	2/100
						ear canal	carcinoma/adenoma	1/97
						stomach	all tumors	1/100
						spinal cord	astrocytoma	0/99
M	0.25^b	26	26	100%^{c}	drinking water	brain	astrocytoma	1/100
						ear canal	carcinoma/adenoma	0/93
						stomach	all tumors	4/97 ($p<0.05$)
						spinal cord	astrocytoma	0/92
M	0.84^b	26	26	100%^{c}	drinking water	brain	astrocytoma	2/100
						ear canal	carcinoma/adenoma	2/88
						stomach	all tumors	4/100 ($p<0.05$)
						spinal cord	astrocytoma	0/98
M	2.49^b	26	26	100%^{c}	drinking water	brain	astrocytoma	10/99 ($p<0.05$)
						ear canal	carcinoma/adenoma	7/94 ($p<0.05$)
						stomach	all tumors	4/100 ($p<0.05$)
						spinal cord	astrocytoma	0/99
M	8.37^b	26	26	100%^{c}	drinking water	brain	astrocytoma	21/99
						ear canal	carcinoma/adenoma	16/93
						stomach	all tumors	1/100
						spinal cord	astrocytoma	4/93
F	0.0	NA	23	NA	NA	brain	astrocytoma	1/199
						ear canal	carcinoma/adenoma	0/193
						stomach	all tumors	1/99
						spinal cord	astrocytoma	1/197
F	0.12^b	23	23	100%^{c}	drinking water	brain	astrocytoma	1/100
						ear canal	carcinoma/adenoma	0/94
						stomach	all tumors	1/100
						spinal cord	astrocytoma	0/97

TABLE 9-6 (cont.)

Sex	Dose or Exposure (mg/kg/day)	Duration of Treatment (months)	Duration of Study (months)	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)
F	0.36[b]	23	23	100%[c]	drinking water	brain	astrocytoma	2/101
						ear canal	carcinoma/adenoma	2/92
						stomach	all tumors	2/100
						spinal cord	astrocytoma	0/99
F	1.25[b]	23	23	100%[c]	drinking water	brain	astrocytoma	4/95 ($p<0.05$)
						ear canal	carcinoma/adenoma	4/90
						stomach	all tumors	2/97
						spinal cord	astrocytoma	1/92 ($p<0.05$)
F	3.65[a]	23	23	100%[b]	drinking water	brain	astrocytoma	6/100 ($p<0.05$)
						ear canal	carcinoma/adenoma	5/94 ($p<0.05$)
						stomach	all tumors	4/100 ($p<0.05$)
						spinal cord	astrocytoma	0/96
F	10.89[a]	23	23	100%[b]	drinking water	brain	astrocytoma	23/98 ($p<0.05$)
						ear canal	carcinoma/adenoma	10/86 ($p<0.05$)
						stomach	all tumors	2/97
						spinal cord	astrocytoma	1/91

QUALITY OF EVIDENCE

Strengths of Study:	The compound was administered for an appreciable portion of the animals' lifespan by a natural route to both sexes at 5 dose levels.
Overall Adequacy:	Adequate

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[a] Bio/dymanics Inc., 1980b; U.S. EPA, 1983a

[b] The dose was calculated from measured water consumption and body weight.

[c] The authors reported that the acrylonitrile was "100% active ingredient".

NA - Not applicable

TABLE 9-7

Incidence in Spartan Rats given Acrylonitrile by Gavage for 19-20 months

Sex	Dose or Exposure (mg/kg/day)	Duration of Treatment (months)	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)
M	0.0	NA	NA	NA	brain Zymbal gland stomach	astrocytoma carcinoma carcinoma/papilloma	2/100 1/96 2/99
M	0.1	19-20	100%^{b}	water	brain Zymbal gland stomach	astrocytoma carcinoma carcinoma/papilloma	0/97 0/93 6/97
M	10	19-20	100%^{b}	water	brain Zymbal gland stomach	astrocytoma carcinoma carcinoma/papilloma	16/98 ($p<0.05$) 10/96 ($p<0.05$) 40/99 ($p<0.05$)
F	0.0	NA	NA	NA	brain Zymbal gland stomach mammary gland	astrocytoma carcinoma carcinoma/papilloma carcinoma	1/99 0/85 2/99 7/101
F	0.1	19-20	100%^{b}	water	brain Zymbal gland stomach mammary gland	astrocytoma carcinoma carcinoma/papilloma carcinoma	2/100 0/94 4/99 6/100
F	10	19-20	100%^{b}	water	brain Zymbal gland stomach mammary gland	astrocytoma carcinoma carcinoma/papilloma carcinoma	17/100 ($p<0.05$) 9/94 ($p<0.05$) 17/99 ($p<0.05$) 22/101 ($p<0.05$)

QUALITY OF EVIDENCE

Strengths of Study:	The compound was administered for an appreciable portion of the animals' lifespan. The group size was large. Extensive histology was performed.
Weakness of Study:	The compound was administered by gavage, allowing transient high levels in the body. Early mortality required shortening the study from 24 months to 19-20 months.
Overall Adequacy:	Adequate

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[a] Bio/dynamics Inc., 1980c

[b] The authors reported that the acrylonitrile was "100% active ingredient".

NA = Not applicable

TABLE 9-8

Incidence of Tumors in Sprague-Dawley Rats Exposed to Acrylonitrile by Inhalation for 24 months

Sex	Dose or Exposure	Duration of Treatment (months)	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence[b] (p value)
M	0.0 ppm	NA	NA	NA	brain/spinal cord	glial cell tumors	0/100
					tongue	all tumors	1/96
					small intestine	benign and malignant	2/99
					Zymbal gland	benign and malignant	2/100
M	20 ppm, 6 hours/day, 5 days/week	24	high purity[c]	in air	brain/spinal cord	glial cell tumors	4/99
					tongue	all tumors	0/14
					small intestine	benign and malignant	2/20
					Zymbal gland	benign and malignant	4/100
M	80 ppm, 6 hours/day, 5 days/week	24	high purity[c]	in air	brain/spinal cord	glial cell tumors	22/99 ($p<0.05$)
					tongue	all tumors	7/89 ($p<0.05$)
					small intestine	benign and malignant	15/98 ($p<0.05$)
					Zymbal gland	benign and malignant	11/100 ($p<0.05$)
F	0.0 ppm	NA	NA	NA	brain/spinal cord	glial cell tumors	0/100
					Zymbal gland	benign and malignant	0/100
					mammary gland	adenocarcinoma	9/100
F	20 ppm, 6 hours/day, 5 days/week	24	high purity[c]	in air	brain/spinal cord	glial cell	8/100 ($p<0.05$)
					Zymbal gland	benign and malignant	1/100
					mammary gland	adenocarc[illegible]	8/100

TABLE 9-8 (cont.)

Sex	Dose or Exposure	Duration of Treatment (months)	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Tumor Type	Incidence[b] (p value)
F	80 ppm, 6 hours/ day, 5 days/week	24	high purity[c]	in air	brain/spinal cord Zymbal gland mammary gland	glial cell benign and malignant adenocarcinoma	21/100 ($p<0.05$) 11/100 ($p<0.05$) 20/100 ($p<0.05$)

QUALITY OF EVIDENCE

Strengths of Study:	Compound administered by a relevant route for the lifespan of the animals to both sexes at 2 concentrations. Extensive histology was performed. The concentration was determined by GC 2-4 times during each exposure. Statiscal analyses were performed.
Overall Adequacy:	Adequate

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[a] Quast et al., 1980b; U.S. EPA, 1983a

[b] The acrylonitrile contained the inhibitor hydroquinone monomethyl ether.

[c] The tumor incidence is expressed as tumors per number of animals examined.

NA = Not applicable

TABLE 9-9

Agent: Acrylonitrile

Reference: Maltoni et al., 1977

Exposure Route	Species/ Strain	Sex	Dose or Exposure	Duration of Treatment (months)	Duration of Study	Vehicle or Physical State	Target Organ	Tumor Incidence
Inhalation	rat/ Sprague-Dawley	M	0.0 ppm	NA	lifespan	NA	total tumors	4/30
Inhalation	rat/ Sprague-Dawley	M	5 ppm, 4 hours/day, 5 days/week	12	lifespan	in air	total tumors	1/30
Inhalation	rat/ Sprague-Dawley	M	10 ppm, 4 hours/day, 5 days/week	12	lifespan	in air	total tumors	10/30
Inhalation	rat/ Sprague-Dawley	M	20 ppm, 4 hours/day, 5 days/week	12	lifespan	in air	total tumors	13/30
Inhalation	rat/ Sprague-Dawley	M	40 ppm, 4 hours/day, 5 days/week	12	lifespan	in air	total tumors	12/30
Inhalation	rat/ Sprague-Dawley	F	0.0 ppm, 4 hours/day, 5 days/week	NA	lifespan	NA	total tumors	9/30

TABLE 9-9 (cont.)

Exposure Route	Species/ Strain	Sex	Dose or Exposure	Duration of Treatment (months)	Duration of Study	Vehicle or Physical State	Target Organ	Tumor Incidence
Inhalation	rat/ Sprague-Dawley	F	5 ppm, 4 hours/day, 5 days/week	12	lifespan	in air	total tumors	17/30
Inhalation	rat/ Sprague-Dawley	F	10 ppm, 4 hours/day, 5 days/week	12	lifespan	in air	total tumors	11/30
Inhalation	rat/ Sprague-Dawley	F	20 ppm, 4 hours/day, 5 days/week	12	lifespan	in air	total tumors	14/30
Inhalation	rat/ Sprague-Dawley	F	40 ppm, 4 hours/day, 5 days/week	12	lifespan	in air	total tumors	8/30

QUALITY OF EVIDENCE

Strengths of Study: compound was administered to both sexes at 4 concentrations by a relevant route for the lifespan of the animals.

Weakness of Study: The duration of exposure was short. The concentrations tested were all below the maximal tolerated concentrations.

Overall Adequacy: Limited

Comments: The author claimed that these results indicated only "a border-line oncogenic effect."

NA = Not applicable; NR = not reported

and 25.5 based on national rates. Of the 25 cases, 8 were respiratory cancer cases vs. 4.4 expected cases based on company rates and 6.1 based on national rates. Excesses were found among workers employed during 1950-1952 (8 cases vs. 2.6 expected; $p<0.01$). During the follow-up period of 1970-1976, there were 6 cases of respiratory cancer vs. 1.5 expected ($p<0.01$). Total cancers for this group were 17 vs. 5.6 ($p<0.01$). In workers with moderate exposures (10-15 ppm) and probable latent periods of ≥ 15 years, the observed and expected numbers of cancer cases were 13 and 5.5, respectively. Half of this excess was due to respiratory cancer, 5 vs. 1.4 ($p <0.05$). As discussed by U.S. EPA (1983a), adjustment for the effects of smoking resulted in 5 observed vs. 1.6 expected ($p <0.05$). Therefore, the relative risk is 5.0/1.6 = 3.1. This study provides limited evidence that acrylonitrile is carcinogenic to humans. Coupled with the sufficient evidence that acrylonitrile is carcinogenic to rats, the data indicate that acrylonitrile is probably carcinogenic for humans; therefore acrylonitrile is classified as a Group 2A chemical according to the system of IARC and B1 in the EPA cancer assessment groups classification system (U.S. EPA, 1984).

Based on the human data from the study of O'Berg (1980), the CAG has estimated from these data that the increased probability of lung cancer associated with each unit increase of acrylonitrile (B_H) is 1.5×10^{-4} $(\text{ppb})^{-1}$ or 6.8×10^{-5} $(\mu g/m^3)^{-1}$. Converting to units of $(mg/kg/day)^{-1}$, assuming a breathing rate of 20 m^3/day for a 70 kg man:

$$6.8\times10^{-5}(\mu g/m^3)^{-1} \times 1\ \text{day}/20\ m^3 \times 1\ \mu g/10^{-3}\ mg \times 70\ kg = 0.24\ (mg/kg/day)^{-1}$$

The dose associated with a lifetime cancer risk of 10% (ED_{10}) is

$$ED_{10} = 0.1/0.24\ (mg/kg/day)^{-1} = 0.42\ mg/kg/day$$

The F factor ($1/ED_{10}$) = 1/0.42 mg/kg/day = 2.4 $(mg/kg/day)^{-1}$

As discussed by U.S. EPA (1983a), the estimation based on the human study is uncertain because of the relatively weak documentation of the exposure estimate.

Alternately, an F factor can be calculated from the dose-response data from animal studies. As discussed in Chapter 8, the U.S. EPA (1983a) calculated a q_1* for acrylonitrile based on the combined incidences of brain and spinal cord astrocytomas, Zymbal gland carcinomas and stomach carcinomas/papillomas in the two drinking water studies of Bio/dynamics, Inc., (1980a,b) and the total tumor incidence in the drinking water study of Quast et al. (1980a). Individual values for q_1* were derived for males and females in the three studies, and geometric means of the male q_1* values and female q_1* values were calculated. The higher geometric mean was recommended as the q_1* for estimating an increased lifetime risk of human exposure by the oral route to acrylonitrile.

Using the same approach, an F factor for acrylonitrile is calculated. The unadjusted values for $1/ED_{10}$ (Tables 9-10 to 9-13) were calculated using the computerized multistage model, GLOBAL 82 (Howe and Crump, 1982). The corrected $1/ED_{10}$ or F factor was calculated by multiplying the unadjusted value by the cube root of the ratio of the human body weight (70 kg) to the rat weight (0.35 kg). For the Bio/dynamics, Inc. (1980a,b) studies, the value was further corrected by multiplying by the cube of the ratio of

TABLE 9-10

Derivation of Potency Factor (F)
Agent: Acrylonitrile

Reference: Quast et al., 1980a

Exposure route: oral

Species: rat

Strain: Sprague-Dawley

Sex: male, female

Vehicle: drinking water

Body weight[a]: 0.35 kg

Duration of treatment: 730 days

Duration of study: 730 days

Lifespan of animal: 730 days

Target organ: multiorgan

Tumor type: all tumors, excluding mammary gland

	Males				Females			
Experimental doses/ exposure (ppm):	0	35	100	300	0	35	100	300
Transformed doses[b]: (mg/kg/day)	0	3.42	8.53	21.18	0	4.36	10.76	24.97
Tumor incidence:	4/80	18/47	36/48	45/48	3/80	24/48	37/48	45/48
Unadjusted $1/ED_{10}$:	1.318543 $(mg/kg/day)^{-1}$				1.2215547 $(mg/kg/day)^{-1}$			
$1/ED_{10}$ (F factor):	7.71 $(mg/kg/day)^{-1}$				7.14 $(mg/kg/day)^{-1}$			

[a] estimated

[b] calculated by investigators

TABLE 9-11

Derivation of Potency Factor (F)
Agent: Acrylonitrile

Reference:	Bio/dynamics Inc., 1980a
Exposure route:	oral
Species:	rat
Strain:	Spartan
Sex:	male, female
Vehicle:	drinking water
Body weight[a]:	0.35 kg
Duration of treatment:	22 months for males, 19 months for females
Duration of study:	22 months for males, 19 months for females
Lifespan of animal:	24 months
Target organ:	brain and spinal cord, Zymbal gland, stomach
Tumor type:	astrocytomas, carcinomas, carcinomas/papillomas

	Males			Females		
Experimental doses/ exposure (ppm):	0	1	100	0	1	100
Transformed doses[b]: (mg/kg/day)	0	0.093	7.98	0	0.146	10.69
Tumor incidence:	6/100	6/98	36/98	1/100	5/100	4/99
Unadjusted $1/ED_{10}$:	0.2857143 $(mg/kg/day)^{-1}$			0.4761905 $(mg/kg/day)^{-1}$		
$1/ED_{10}$ (F factor):	2.17 $(mg/kg/day)^{-1}$			5.61$(mg/kg/day)^{-1}$		

[a] estimated

[b] calculated by investigators

TABLE 9-12

Derivation of Potency Factor (F)
Agent: Acrylonitrile

Reference:	Bio/dynamics Inc., 1980a
Exposure route:	oral
Species:	rat
Strain:	Fischer 344
Sex:	male
Vehicle:	drinking water
Body weight[a]:	0.35 kg
Duration of treatment:	26 months
Duration of study:	26 months
Lifespan of animal:	24 months
Target organ:	brain and spinal cord, Zymbal gland, stomach
Tumor type:	astrocytomas, carcinomas, carcinomas/papillomas

Experimental doses/ exposure (ppm):	0	1	3	10	30	100
Transformed doses[b]: (mg/kg/day)	0	0.11	0.25	0.81	2.49	8.15
Tumor incidence:	5/200	4/100	5/100	7/100	20/100	34/100

Unadjusted $1/ED_{10}$:	0.5263158 $(mg/kg/day)^{-1}$
$1/ED_{10}$ (F factor):	3.08 $(mg/kg/day)^{-1}$

[a] estimated

[b] calculated by investigators

TABLE 9-13

Derivation of Potency Factor (F)
Agent: Acrylonitrile

Reference:	Bio/dynamics Inc., 1980a					
Exposure route:	oral					
Species:	rat					
Strain:	Fischer 344					
Sex:	male					
Vehicle:	drinking water					
Body weight[a]:	0.35 kg					
Duration of treatment:	23 months					
Duration of study:	23 months					
Lifespan of animal:	24 months					
Target organ:	brain and spinal cord, Zymbal gland, stomach					
Tumor type:	astrocytomas, carcinomas, carcinomas/papillomas					
Experimental doses/ exposure (ppm):	0	1	3	10	30	100
Transformed doses[b]: (mg/kg/day)	0	0.12	0.36	0.82	3.65	10.89
Unadjusted $1/ED_{10}$:	0.3703704 $(mg/kg/day)^{-1}$					
$1/ED_{10}$ (F factor):	2.46 $(mg/kg/day)^{-1}$					

[a] estimated

[b] calculated by investigators

the lifespan of the rat to the duration of the study. The F factors and the geometric means are summarized in Table 9-14. The higher of the two geometric means, 4.62 $(mg/kg/day)^{-1}$, is taken as the F factor. Since the F factor is between 1 and 10, acrylonitrile is placed in Potency Group 3. A Potency Group 3 chemical with an IARC classification of 2A ranks medium in the Hazard Ranking Scheme uncer CERLA.

TABLE 9-14

F Factors for Three Drinking Water Studies in Rats

F Factor (mg/kg/day)		
Males	Female	References
7.71	7.14	Quast et al., 1980a
2.17	5.61	Bio/dynamics Inc., 1980a
3.08	2.46	Bio/dynamics Inc., 1980a
3.72	4.62	Geometric Mean

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Young, J.D., R.W. Slauter and R.J. Karbowski. 1977. The pharmacokinetic and metabolic profile of ^{14}C-acrylonitrile given to rats by three routes. Prepared by the Toxicology Research Laboratory, Health and Environmental Research, Dow Chemical USA, Midland, MI, for the Chemical Manufacturers Association, Washington, DC.

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Zitting, A., R. Tenhunen and H. Savolainen. 1981. Effects of intraperitoneally injected acrylonitrile on liver, kidney and brain. Acta Pharmacol. Toxicol. 49(5): 412-415.

Appendix A

This profile is based on data identified by computerized literature searches of the following:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP

These searches were conducted in Febuary and March, 1985. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values. 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983). Cincinnati, OH. 486 p.

ACGIH (American Conference of Governmental Industrial Hygienists). 1984. TLVs: Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1984-1985. Cincinnati, OH. 94 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology. 3rd rev. ed. Vol. 2A. John Wiley and Sons, NY. 2878 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology. 3rd rev. ed. Vol. 2B. John Wiley and Sons, NY. p. 2879-3816.

Clayton, G.D. and F.E. Clayton, Ed. 1982. Patty's Industrial Hygiene and Toxicology. 3rd rev. ed. Vol. 2C. John Wiley and Sons, NY. p. 3817-5112.

Grayson, M. and D. Eckroth, Ed. 1978-1983. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology. 3rd ed. Publishing Sciences Group, Inc., MA. 575 p.

IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. IARC, WHO Lyons, France.

ITII (International Technology Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

NTP (National Toxicology Program). 1985. Toxicology Research and Testing Program. Chemicals on Standard Protocol. Management Status.

Ouellette, R.P. and J.A. King. 1977. Chemical Week Pesticide Register. McGraw-Hill Book Co., NY.

Sax, I.N. 1979. Dangerous Properties of Industrial Materials. 5th ed. Van Nos Reinhold Co., NY.

SRI (Stanford Research Institute). 1984. Directory of Chemical Producers. Stanford, CA.

U.S. EPA. 1982. Chemical Activities Status Report. 3rd ed. (EPACASR). Offices of Pesticides and Toxic Substances, Washington, DC. EPA 560/TIIS-82-002b.

U.S. EPA. 1983. Status Report on Rebuttable Presumption Against Registration (RPAR) or Special Review Process. Registration Standards and the Data Call in Programs. Office of Pesticide Programs, Washington, DC.

U.S. EPA. 1984. CSB Existing Chemical Assessment Tracking System. Name and CAS Number Ordered Indexes. Office of Toxic Substances, Washington, DC.

USITC (United States International Trade Commission). 1983. Synthetic Organic Chemicals. U.S. Production and Sales, 1982, USITC Publication 1422. Washington, DC.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals. 2nd ed. Van Nostrand Reinhold Co., NY.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. United States Dept. Interior, Fish and Wildlife Service. Resource Publ. 137. Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria. 2nd ed. Prepared for the Resources Agency of California. State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effect of Pesticides on Non-Target Species. PB-269605. Prepared for the U.S. EPA, Washington, DC.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. EPA 540/9-79-003 NTIS PB 80-196876. Office of Pesticide Programs. U.S. EPA. Washington, DC.

In addition, the following FYI submissions were obtained. A review of these submissions on microfiche revealed that some were duplicates of chemical company studies that had already been received as hard copies and are cited in this profile. Others were not useful.

FYI-AX-0380-0073
0480-0073
0481-0073

FYI-AX-1179-0047

FYI-OTS-0477-0150
0677-0150

FYI-OTS-1182-0217

FYI-OTS-0283-0235